Responses to Major Comments on Technical Support Document

Public Health Goal
For
PERCHLORATE
In Drinking Water

Prepared by

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INTRODUCTION

The following are the responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on several drafts of the proposed public health goal (PHG) technical support document for perchlorate. The comments and responses here are separated into three parts, corresponding to comments on the pre-release draft; on the first public review draft (received at and shortly after (45 days) the PHG workshop held on April 29, 2002; and comments on the second public review draft.

Comments from University of California peer reviewers were received on the pre-release draft and on the second public review draft. Comments from the U.S. Environmental Protection Agency (U.S. EPA) were received on all three drafts. Several other reviewers commented multiple times on the two public release drafts, and sometimes identical comments were submitted multiple times by the same or other reviewers. For the sake of brevity, we have selected the more important or representative comments from each reviewer for responses.

Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics. The comments were reviewed and taken into consideration when they were received. However, the responses to the comments presented here reflect the changes made to the final document after consideration of the additional comments received during the second comment period and the UC peer review.

Although required by Health and Safety Code Section 116365(c)(2)(C) and a court order in related litigation, these written comments and responses are provided in the spirit of the open dialogue among scientists that is part of the general peer review process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments on the Pre-release Draft

Comments from University of California, San Francisco (first peer review)

Comment 1: "This is an excellent review of the chemistry, occurrence, metabolism and toxicology of perchlorate. The review is very comprehensive, including references to studies of perchlorate as far back as 1952 and as recent as 2000, covering almost 50 years."

Response 1: No changes are needed.

Comment 2: "The studies of perchlorate toxicity in animals (rats, mice and rabbits) were helpful in understanding the mechanism of action of perchlorate, which blocks the uptake of iodine by the thyroid gland producing goiter and hypothyroidism. However the human studies were much more relevant in developing a Public Health Goal for perchlorate in drinking water. The report emphasizes, appropriately, that pregnant women on a low iodine diet, and their fetuses, present a very sensitive sub population for whom a high level of perchlorate in the water could be very detrimental."

Response 2: We agree; no changes are needed.

Comment 3: "The authors have carefully analyzed the human data to calculate the minimal amount of perchlorate which could produce an adverse effect. They propose that the Public Health Goal of 6 mcg/L, or 6 ppb, would be a level of perchlorate in drinking water which would protect the general population and the sensitive subgroup from any adverse effects of perchlorate. Their calculations include a generous "uncertainty factor" to be certain that the recommended level is safe. I agree with their calculations and their recommendations."

Response 3: No changes are needed in response to this comment. However in the final document, the uncertainty factor was reduced because a different human study data set was used, and a benchmark dose approach was used instead of the LOAEL/NOAEL approach to analyze the data, providing the same result by a different calculation method.

Comments from University of California, Riverside (first peer review)

Comment 1: "The "Public Health Goal for Perchlorate in Drinking Water" document is a generally well written and thought out overview of the toxicity and health risks associated with consuming water contaminated with perchlorate. The derivation of the

PHG from a NOAEL in combination with the use of uncertainty factors is a standard risk assessment approach, and seems to be appropriate given the information available for this chemical, and current regulatory policies. However, the risk assessment is somewhat unusual in that the PHG is based upon a short-term perchlorate-induced reduction in iodine uptake in humans which, if it persists for a prolonged period, is believed to result in a decrease in thyroid hormone levels. If this occurs in a pregnant woman with marginal to inadequate iodine intake, the developing fetus and infant will be at higher risk for abnormal neuropsychological development. The postulated outcomes are serious and have a solid mechanistic link to thyroid deficiency in humans. However, the connection of neuropsychological effects to low level perchlorate exposure, while likely, is contingent upon a number of conditions and has not been directly shown. For most chemicals, the number of individuals who would be affected based upon the proposed scenario would likely be small. However, because of the widespread exposure to perchlorate and the prevalence of iodine deficiency, I believe that OEHHA is justified in considering these effects."

Response 1: No changes required.

Comment 2: "The primary study that was selected for the derivation of the PHG was a study reported by Lawrence *et al* (2000) where a decrease in the uptake of I^{123} by the thyroid was seen in male volunteers administered 10 mg of perchlorate. ... Lawrence and associates (Lawrence, *et al.*, 2001) have recently reported the results of a similar study in which a daily dose of 3 mg perchlorate was administered to 8 male volunteers. Modest non-significant decreases (approx. 10%) in thyroid radioactive iodine uptake were seen. I would recommend including this new study in the document to modify the LOAEL/NOAEL. Two approaches would seem acceptable. One would be to use the new value as a LOAEL and then apply an uncertainty factor of two (or three) to estimate a modified NOAEL. Because of the modest nature of the observed effects, I believe that such an UF would be justifiable. Alternatively, a NOAEL could be estimated by regression using the two data points similar to the approach used by Greer *et al.* (2000). In addition, I would contact Greer and associates to request an expanded report of the data presented in their abstract. I would then use this as a second estimate for the NOAEL. Since the two would be independent estimates of the NOAEL, I would recommend averaging the estimates to derive a composite NOAEL. Based on my rough calculations, the estimates from the two groups should be quite similar."

Response 2: The new study was added to the draft that went out for the initial public comment period and workshop. It incorporated the averaging approach recommended by the commenter. However, in the public comments received, it became clear that the Greer *et al*. (2002) study was far superior to the Lawrence *et al*. (2000 and 2001) studies as it has more dose groups, a strict dosing schedule, and included doses lower than those used in the Lawrence *et al*. studies. In its final version, the PHG was determined by the benchmark dose approach using the thyroidal iodide uptake data reported by Greer *et al.* (2002).

Comment 3: "Three uncertainty factors were used to derive the PHG – a 10X factor for converting a LOAEL to a NOAEL, a 3X factor due to the quality of the data upon which the LOAEL was derived, and a 10X factor for inter-individual variability. I believe that the first can be eliminated by using the results of the Lawrence *et al.* (2001) and the Greer *et al* (2000) studies. However, the end result will be very similar. Secondly although the studies are less than ideal, I believe that OEHHA should consider reducing or eliminating the 3X UF because there are multiple human studies providing similar LOAEL and NOAEL values. In addition, the reduction in radio-iodine uptake represents a sensitive marker which would precede a decrease in thyroid hormone levels in the subjects at risk. The 10X factor for inter-individual variability is standard and should be retained. Ordinarily based on the nature of the sensitive populations identified, I would recommend an additional UF. However, given that iodine uptake is a sensitive endpoint and likely to occur at lower concentrations than any change in thyroid hormone levels, I would estimate that the 10× inter-individual factor would be adequate."

Response 3: The 10-fold uncertainty factor for converting a LOAEL to NOAEL was eliminated as suggested by the commenter. In the final document, a benchmark dose approach was used in evaluating the thyroidal iodide uptake data from the Greer *et al.* (2002) study. The 3-fold uncertainty factor for the limitation of the database was also removed because of the sensitive nature of the critical endpoint selected. Also, there are limited clinical and occupational data regarding long-term exposure to perchlorate. In the final document, an uncertainty factor of 10 was applied to account for interindividual variability.

Comment 4: "I would also recommend comparing the derived PHG against the perchlorate concentrations in drinking water from Clark and other counties that have been evaluated in ecologic epidemiological studies without detecting an increase in hypothyroidism {see examples in the document as well as the new study by (Li, *et al.*, 2001)}. Although there are weaknesses in ecological studies, I believe that these can be justifiably used as a benchmark against which to compare a proposed PHG. If there are serious discrepancies between the estimates, I would re-examine the estimates and the uncertainty factors."

Response 4: Li *et al*. (2000) studied neonatal blood TSH levels sampled between December 1998 and October 1999 in Las Vegas (with up to 15 ppb perchlorate in drinking water) and in Reno (with no perchlorate in drinking water). The authors found that neonatal TSH levels were not associated with perchlorate exposure of less than or equal to 15 ppb ($p=0.97$). However, the lack of control of a number of variables that are known to affect serum T4 and TSH levels in infants, such as age at sampling, birth weight, and ethnic origin, makes interpretation of the results difficult. In addition, the exclusion of infants less than 2.5 kg or more than 4.5 kg might have impacted the results. Neonatal blood TSH levels may not be impacted even though the fetus had been affected.

Comment 5: "I believe that additional justification should be provided for the 40% value selected for the relative source contribution. While I realize that an extensive review on

the use of perchlorate in fertilizers and the uptake of perchlorate by the edible portion of plants is outside the scope of this document, some discussion should be provided as the rationale for the selection of the relative source contribution."

Response 5: We are required to consider multi-pathway exposure in PHG development. The standard procedure we use is based on U.S. EPA precedents, with a default value between 0.2 and 0.8. The relative source contribution has been changed to 60 percent (0.6 in the calculation). Though comprehensive food survey data are not available, there have been reports of detecting perchlorate in lettuce, cucumber, strawberry, grass, cow's milk, and human breast milk (Kirk *et al*., 2003; Smith and Jackson, 2003).

Comment 6: "I would agree that pregnant women with marginal to inadequate iodine intake and their developing fetuses and infants would constitute the groups of most concern. Although these groups have been identified, it is not clear how this information has been used to modify the risk estimated in the document. Some adjustment would seem appropriate, although as indicated above, these groups would probably be protected using the 10X UF for inter-individual variability. There is another area of enhanced susceptibility that has not been mentioned in the document that I believe should be discussed. In mammals, iodide transfer through breast milk is necessary for thyroid hormone synthesis by the newborn. Perchlorate inhibits the sodium iodide symporter in the mammary gland and significantly interferes with the transfer of iodide into breast milk (Perron, *et al.*, 2001). This reduction in iodide transfer has been seen in dairy animals (cows and goats) (Howard, *et al.*, 1996; Lengemann, 1973; Mountford, *et al.*, 1987) as well as laboratory rodents (Yu, *et al.*, 2001). These effects have also been seen at low levels (0.1 mg/kg-day in rats (Narayanan, *et al.*, 2001); 10-50 mg/cow (Lengemann, 1973) and 100 mg/goat (Mountford, *et al.*, 1987)[1]). Since the sodium iodide symporter appears to be highly conserved across species (Perron, *et al.*, 2001), these results are likely to be directly relevant to humans."

Response 6: Identification of the fetus as one of the sensitive populations and the concern for adverse neurodevelopmental effects help to place many studies into context. For example, as discussed above, ecological studies evaluating neonatal serum TSH levels would not address all the concerns for the fetus. Furthermore, while effects on serum TSH level may be reversible, adverse neurodevelopmental effects on the fetus may be irreversible. This information on the sensitive subpopulations also allowed us to select the appropriate body weight, water consumption rate and source contribution for these subpopulations.

It is known that perchlorate at high doses inhibits iodide secretion into milk in farm animals. The reduction of iodide in breast milk is a health concern and that is one of the reasons why the PHG is set at a level that will prevent significant inhibition of NIS. Assuming the NIS in mammary gland tissue is functionally similar to NIS in thyroid tissue, a perchlorate dose that does not inhibit NIS in thyroid tissue is also not likely to inhibit NIS in mammary gland tissue. Most of the suggested references have been added to the document.

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[1] These numbers were estimated from abstracts and need to be verified.

Comment 7: *Two other sensitivity issues deserve to be mentioned:* "1) Large numbers of Americans are reported to exhibit abnormal thyroid function (Canaris, *et al.*, 2000) and may also represent a group with elevated susceptibility. 2) The increased water consumption of small children may also be a concern particularly in formula-fed infants or after breast-feeding has ended."

Response 7. We agree that the large number of individuals with abnormal thyroid function should be identified as a sensitive population. The document has been revised accordingly. The issue of increased water consumption of small children and formula-fed infants is an important one. The document has been revised to specifically address this issue. Though the kinetics of absorption and excretion of infants and rat pups are certainly not identical, in the physiologically based pharmacokinetic modeling results reported by Clewell *et al*. (2003), they estimated that the rat pup receives a greater perchlorate dose than the dam when adjusted for body weight, up to sevenfold greater at the lowest perchlorate dose in their study. However, serum perchlorate levels (expressed as area under the curve) in neonatal rats drinking their mother's milk were slightly lower than those of male rats, pregnant rats, and lactating rats, which probably reflects increased excretion offsetting the increased intake. Similar detailed pharmacokinetic estimates are not available for human infants consuming their mother's milk or formula made from perchlorate-contaminated water, so we must acknowledge the potential for greater exposure of infants while being uncertain about the effective dose (area under the curve).

Comment 8: "Given the different levels of thyroid hormones and binding proteins in the rats and humans and the challenges in interpreting the results of the rat studies, I would agree that the use of human studies is clearly preferable for quantitative estimates to establish the PHG. In addition, since disruption of the thyroid-pituitary axis appears to be critical for thyroid carcinogenesis induced by perchlorate, a PHG that protects against changes in thyroid hormone levels and radio-iodine uptake should also protect against thyroid cancer."

Response 8: OEHHA agrees with the conclusions of this peer reviewer. No changes are needed.

Comments from University of California, Davis (first peer review)

Comment 1: "A relative source contribution of 40% for perchlorate in water is used to account for uptake of perchlorate from food rather than water. It is not clear where the 40% source contribution number comes from (nor is an explanation of this number presented), as the document states "there are currently no data available regarding the level of perchlorate contamination of food produced in California…." A single (two-page long) reference (Renner, 1999) is cited elsewhere in the document reporting bioaccumulation of perchlorate in lettuce, but given the high aqueous solubility of perchlorate it is an unlikely candidate for bioaccumulation. Thus, the source attribution

of 60% of total perchlorate intake to contaminated vegetables and other undefined sources seems much too high, and a source attribution to water of 80%, as used in the Federal EPA risk assessment, seems a good deal more reasonable."

Response 1: Information is inadequate to accurately calculate relative exposures from water versus other sources of perchlorate. The value of relative source contribution (RSC) was increased to 80 percent in the second draft when questions were raised about the reliability of the data mentioned above concerning perchlorate in lettuce. In the final PHG document, the RSC has been revised to 60 percent.

The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types.

Comment 2: "Suitability of defaults: The use of factors of 10 to account for LOAEL to NOEL extrapolation and inter-individual variability are standard methods in risk assessment and are used correctly herein. The uncertainty factor of three to compensate for the poor quality of the data set used is a red flag, and raises obvious questions about whether this is the best choice of study on which to base the risk assessment."

Response 2: Since the Greer *et al*. (2002) study is now available on which to base a point of departure, a LOAEL-to-NOAEL uncertainty factor is no longer needed. Based on the animal and human toxicity data available, OEHHA believes inhibition of thyroidal iodide uptake in humans, while based on a less than perfect data set, is superior to other alternatives. The uncertainty factor of three to account for database limitation is no longer applied in the final risk assessment.

Comment 3: "For reference purposes, the proposed PHG of 6 ppb in drinking water would correspond to a dose (assuming consumption of 2 liters per day) of 12 µg/per day, a dose about 1000-fold lower than that in the Lawrence *et al.* (2000) study. Clearly issues of whether there is or is not a threshold for the adverse effects of perchlorate on iodide absorption by the thyroid arise, and clearly the answer to this question must be yes, as perchlorate is a competitive inhibitor of iodide uptake. It is also pertinent that

upon removal of the perchlorate from the subject's drinking water in the cited study, thyroid iodine uptakes had rebounded to 25% above baseline values 14 days later, indicating complete reversibility of the inhibitory effect of perchlorate. No evidence of hypothyroidism was observed in these subjects, nor were effects observed on serum TSH or circulating levels of thyroid hormones, even at these relatively very high concentrations of perchlorate in drinking water."

Response 3: The Lawrence *et al.* (2000) study suffers from a number of limitations: (a) small sample size, (b) only male subjects, (c) only one dose group, and (d) daily dosing schedule was not controlled and might be different for various subjects. A similar human study reported by Greer *et al*. (2002) overcomes most of these limitations. Applying the benchmark dose approach to the Greer *et al.* (2002) inhibition of thyroidal iodide uptake data, OEHHA determined a lower confidence limit on the five percent reduction in thyroidal iodide uptake (a BMDL of 0.0037 mg/kg-day) as the point of departure.

When the perchlorate exposure exceeds the threshold, it may take weeks or even months of inhibition of thyroidal iodide uptake before serum levels of T3, T4 and TSH would be impacted. The duration may vary from person to person depending on the degree of inhibition, dietary iodide intake level, and the amount of iodide stored in the thyroid. Although the effects of perchlorate on thyroid uptake should be reversible, effects of low maternal T4 on fetal neurodevelopment are not.

Comment 4: "Pages 46-51 of the draft PHG discuss developmental and reproductive endpoints in populations exposed to perchlorate in drinking water. In the first study mentioned a group of pregnant women were administered 600-1000 mg of potassium perchlorate per day (Crooks and Wayne, 1960). One of 12 infants born to these women had a very slightly enlarged thyroid gland, and it returned to normal size within 6 weeks; no other abnormalities were observed. The obvious conclusion from this study is that gross effects of perchlorate in utero on the fetal thyroid gland appear to be relatively minor and to also be reversible upon removal of exposure to these very high levels of perchlorate (100,000 times higher than the proposed PHG). Four more recent studies have explored whether there is an association between perchlorate exposure and thyroid function in newborn infants and children. Three of these studies are negative; concentrations of perchlorate below 100 µg/liter did not appear to affect thyroid function in newborns or children (Crump *et al.*, 2000; Li *et al.*, 2000; Lamm and Doemland, 1999). The fourth study, which reported effects of exposure to perchlorate, contained methodological flaws that make it unsuitable for use as the basis for a quantitative risk assessment, as discussed in the document (Brechner *et al.*, 2000). Also, the study by Lieberman *et al.* (1998) showing no decrease in levels of serum inorganic iodine during pregnancy suggests that the developing fetus is not usually subjected to an abnormal stress during pregnancy. In fact, serum concentrations of T4 are higher in the first trimester than normal levels, and TSH is not depressed in the first trimester of pregnancy either (Lieberman *et al.*, 1998)."

Response 4: Crooks and Wayne (1960) administered potassium perchlorate at 600 to 1,000 mg/day to a group of pregnant women that were suffering from hyperthyroidism and observed a very slightly enlarged thyroid in 1 of the 12 infants born to the mothers.

The fact that the women were initially hyperthyroid makes the extrapolation of this study result to the general population difficult. Neurological development of the offspring was not evaluated in the study. One cannot conclude that the effects of perchlorate in utero are relatively minor and reversible based on this study.

None of the four ecological studies mentioned (Crump *et al.*, 2000; Li *et al.*, 2000; Lamm and Doemland, 1999; Brechner *et al.*, 2000) investigated the potential association between perchlorate exposure during pregnancy and adverse neurological development (IQ reduction) in the offspring. Congenital hypothyroidism, serum T4 depression, and serum TSH elevation may not be the most sensitive indicators of perchlorate effect on fetuses and infants. Insufficient exposure data and the lack of control of some of the confounding factors also make interpretation of these studies difficult. Consequently, these study results were deemed unsuitable for use as the basis for quantitative risk assessment, and the document has been revised to clarify this point.

Lieberman *et al.* (1998) studied the serum T4, thyroglobulin, and TSH levels in 16 women during pregnancy and after delivery. They found serum T4 levels were significantly higher in all three trimesters than those after delivery. However, it is important to note that the iodine intake of the subjects was very high, approximately 600 µg/day. The mean urinary iodine (477-809 µg/g creatinine) measured in these women is many times higher than that reported in a national survey (median urinary iodine for child-bearing age women was 113 µg/g creatinine; Hollowell *et al.*, 1998). Changes in thyroid hormone levels during pregnancy in women with low iodine intake or those with hypothyroidism are likely to be different from those reported in this paper. In their report, Lieberman *et al.* (1998) stated, "reports from iodine-deficient regions indicate that maternal thyroid hormone deficiency is aggravated as gestation proceeds."

Comment 5: "There are several animal studies described in the draft PHG that would allow for quantitative interpretation of the data. Perhaps the best and most relevant of these is a 14 day study in female rats described in Table 6b and the third paragraph of page 18. The relevant endpoint is follicular cell hypertrophy, and the observed NOEL is 1 mg/kg/day. We will assume two uncertainty factors of 10, for interspecies extrapolation and for susceptible individuals, and an additional uncertainty factor of three for 14 day to chronic extrapolation. In addition, we can assume an average body weight for women of 50 kg, a consumption of 2 liters of water per day, and a source allocation of 50% (probably too conservative) of perchlorate intake to drinking water. With all of these assumptions, I would calculate an appropriate drinking water PHG for perchlorate of about 40-50 ppb. Were a source allocation of 80% to drinking water to be used (see above), the PHG would increase to 64-80 ppb. OEHHA might want to consider this approach. At the very least, they should explicitly explain why they chose a very weak data set on iodide uptake in 9 male humans for setting this standard in preference to a reasonably good quantitative study in female animals with the highly relevant (and sensitive) endpoint of direct histological effects on the thyroid."

Response 5: The report available to the peer reviewer contained a limited number of animal studies. Since that time U.S. EPA (2002) released additional animal data results. In their report, U.S. EPA (2002) reviewed and evaluated the animal toxicity data and

determined a LOAEL of 0.0085 mg/kg-day, based on several thyroid-hormone related endpoints, including the brain morphometric changes observed in a rat developmental neurotoxicity study (Argus Laboratories, 2001). This LOAEL of 0.0085 mg/kg-day is substantially lower than the one identified by the reviewer in our draft report, 1 mg/kg-day. Consequently, it is clear that the endpoint identified by the reviewer was not the most sensitive endpoint based on available information.

With the data available, it is difficult to quantify the uncertainty associated with the inter-species extrapolation. It is believed that rodents are more sensitive than human adults to the perturbation of thyroid hormone homeostasis from short-term perchlorate exposure. For these reasons, OEHHA chooses to use human toxicity data instead of the animal data in developing a PHG for perchlorate. Benchmark dose modeling was applied to the thyroidal iodide uptake data (37 subjects in four dose groups) reported by Greer *et al.* (2002) for the development of the PHG in the final document.

Comment 6: "The correct figure for median urinary iodine concentration cited should be 15.3 +/- 1.0 for the western U.S., not the national median of 14.5 cited. California is a western state. The correct figure for urinary iodine concentration below 5 µg/dL cited should be 6.9 +/- 1.9% for the "known pregnant" women, not 14.9% for women of childbearing age. The chosen numbers cited tend to inflate the risk as opposed to appearing to objectively estimating the risk. There is also a huge discrepancy between the NHANES I and III studies, performed in 1971-1974 and 1988-1994, respectively. The putative iodine deficiency apparently increases by a factor of 7 over this interval (e.g., number of known pregnant women with urinary iodine concentration <5 µg/dL is 1.0 +/- 0.6 in NHANES I). This discrepancy is glossed over by an assumption that salt ingestion dropped voluntarily over this interval, but that is unlikely to account for differences of this magnitude. It is pivotal to the risk assessment and the assumption of pregnant women as a susceptible population that the size of this population at risk is ascertained accurately, and it is not clear that these NHANES studies do so."

Response 6: The data for western states have been added to the PHG document as suggested by the reviewer. The iodide status of the child-bearing subgroup was chosen instead of the value associated with the "known pregnant" subgroup because OEHHA regards the child-bearing subgroup as the women potentially at risk. The "known pregnant" subgroup represent only those who are at risk at the time of the survey. OEHHA acknowledges that there is a huge difference between the NHANES I and III results, and that the causes of this difference are unclear. While better refinement of this issue would be helpful, it would not quantitatively change the risk assessment. The values reported from NHANES were to inform the reader and were not specifically used in the PHG calculation.

Comment 7: "The toxic effects of perchlorate are clearly related to its competitive inhibition of iodide uptake into the thyroid gland, which in turn is related to the iodine nutritional status of the individual exposed to perchlorate. The higher the level of endogenous iodine in the diet, and therefore in the thyroid, the less toxic effect would occur upon exposure to perchlorate in drinking water. Thus, a rational public health

strategy might focus not only on the regulation of perchlorate levels in drinking water, which is obviously a necessary goal, but also on insuring an adequate dietary intake of iodine in the general population. If iodized salt is not an adequate and sufficient strategy to maintain optimal levels of iodine in the diet of all Californians, then perhaps exploring enrichment of bread, water softener salt, and/or other ubiquitous dietary components with iodide should be explored. Clearly, there will be a threshold for any putative adverse effects of low levels of perchlorate in drinking water, and this threshold will depend upon the concentration of perchlorate in the water and upon the iodine nutritional status of the individual drinking the water. Linear extrapolation from ingestion of high doses of perchlorate to chronic effects of low doses below that at which biological effects are observed must be justified in this context; the proposed PHG fails to do this."

Response 7: The adverse health effects of perchlorate are expected to be affected by the dietary iodide intake and thyroidal iodide reserve; however, there are no data that can be used to quantify the relationship. It should be noted that the human subjects in the studies reported by Lawrence *et al.* (2000, 2001) and Greer *et al.* (2002) had relatively high dietary iodide intake.

OEHHA agrees that it is a sound public health policy to ensure an adequate dietary intake of iodine in the general population. However, such a policy is not within the jurisdiction of the California Environmental Protection Agency. Furthermore, our responsibility is to assess the risk to Californians and not to identify risk management strategies such as encouraging a potentially affected population to take a supplement to counter the adverse health effects of an environmental pollutant, rather than controlling the pollutant.

Comment 8: "The chosen study for the risk assessment in the proposed PHG is probably not the best choice of data set available. The susceptible population for which this PHG is selected is women and their developing fetuses, yet the study chosen is a study performed only in men. Ideally, a very large epidemiological study in California women of child-bearing age would be most likely to yield definitive results. Absent this, a quantitative study in female rats discussed above seems the best choice of those studies already available. There should be more discussion in the PHG as to why OEHHA chose the data set they did, and what the implications of using alternative data sets on the PHG might be."

Response 8: In the absence of the well-designed epidemiological study suggested by the commenter, OEHHA used the drinking water studies reported by Greer *et al.* (2002) for the determination of a PHG for perchlorate in the final document. Both male and female subjects participated in this study. The PHG document has been substantially revised to explain why the Greer *et al*. (2002) study was preferred over the animal toxicity studies. Most of the peer reviewers agree with OEHHA on the selection of the critical study.

Comments from U.S. Environmental Protection Agency Office of Research and Development and Office of Water

Comment 1: "We commend you on a well-written and logical presentation of the important aspects of perchlorate toxicity. The PHG document reads easily and the tabular presentation of critical data supports summary statements in the text. The parity between the topics presented under the laboratory animal toxicity and the human, with the exceptions with respect to mode of action noted below, affords considerable clarity to communicating the key areas of concern. ... A particularly useful contribution to the conversation on perchlorate that this document offers is the more detailed discussion of iodide deficiency and the potential similarities between its effects and that of perchlorate inhibition of iodide uptake and the sodium-iodide (Na^+-I^-) symporter (NIS)."

Response 1: No response needed.

Comment 2: "[W]e do have concern that the differences in the quality and level of resolution of the predominantly historical and clinical studies found in the iodide deficiency database are not discussed. This discussion would provide a better appreciation of the database in its entirety and the limitations of the human data when used to integrate the diverse sets of contemporary data on the toxic effects of perchlorate across species. Further, we are concerned that the toxic effects of perchlorate exposure are equated with iodide deficiency as a disease state."

Response 2: Limitations of some of the ecological studies are added in the final document. Based on the mechanistic and toxicity information available, adverse health effects caused by perchlorate at low doses are similar to those associated with iodide deficiency. However, the document has been revised to clarify the health effects of concern, neurodevelopment of fetuses and thyroid enlargement in pregnant women.

Comment 3: *Key events related to the mode of action of perchlorate seem inadequately addressed and not organized in a conceptual framework that would lead the reader to a clearer understanding of perchlorate toxicology and risk assessment.* "If the PHG document instead provided a mode of action framework and the "carcinogenicity" data were relocated and re-labeled as a "chronic toxicity" section preceding that on genetic toxicity, it would be easier to appreciate the relationship between thyroid hormone economy, hyperplasia and tumor development."

Response 3: After extensive revisions, we believe that the mode of action discussion in the final document is clearer. The organization of sections has been retained.

Comment 4: "The lack of mode of action framework to tie observed effects together is also evident elsewhere in the PHG document. "Endocrine toxicity" is called out separately in the human section. Despite endocrine effects in the laboratory animals, no section for parity exists. There is separate entry entitled "physiological/nutritional role", but this is actually an indirect effect of perturbation of the hypothalamic-pituitary-thyroid axis by competitive inhibition of iodide uptake at the NIS. Perchlorate was used to

"fatten" animals because hypothyroid animals become obese due to slowed metabolism. This section could be readily incorporated into a more general section on mode of action and not call attention to these historical practices."

Response 4: The section on "physiological/nutritional role" has been deleted and a section on "endocrine toxicity" has been added to the animal section in the final document.

Comment 5: "A critical clarification is important to keeping the PHG document commensurate with the state-of-the-science in risk assessment. The thyroid tumor assessment guidance (Table 43 in PHG document) was directed at species comparisons with respect to the propensity to develop tumors. Careful consideration is required to use this guidance for a more generalized species comparison of anti-thyroid effects. For example, potential differences in rodents versus humans (Page 17 and Page 82) in the PHG document is portrayed as a difference in *regulation*. This is not correct. As already noted, there is striking similarity, likely due to conservation of this important feedback system, in the regulation of the hypothalamic-pituitary-thyroid axis. Circulating levels of thyroid hormones feed back to upregulate TSH in all species. The quantitative differences of the dynamics of the system are due to the difference in plasma protein binding of the thyroid hormones (T4 and T3) in the circulating blood and the resultant effect on colloid stores in the thyroid."

"Humans have greater stability of plasma protein binding (thyroglobulin versus albumin) and larger stores of colloid (intrafollicular storage of thyroid hormone). Critical evaluation of these differences is required when discussing potential dose metrics and neurodevelopmental versus neoplastic sequelae. The temporal and quantitative dosimetry with respect to the mechanism of competitive inhibition of iodide by perchlorate at the NIS must be appreciated to avoid statements that may be easily misinterpreted in the regulatory risk assessment arena, such as that on Page 88: *Humans appear to be less sensitive than rats to the thyroid-hormone disrupting effect of perchlorate*. This statement does not recognize the difference between the first key mechanistic event, inhibition of iodide uptake at the NIS, versus downstream events such as hyperplasia and neoplasia due to subsequent upregulation of TSH. Further, it would not be public-health protective to assume that the entire population has stores of colloid - those with hypothyroidism (or iodide insufficiency) may not and may be more susceptible to perchlorate exposure."

Response 5: The negative feedback mechanism used in regulating thyroid hormones is similar in rodents and in humans. There are significant and important quantitative differences in the sensitivity of the system to anti-thyroid effects of perchlorate. Though the sensitivities of human and rodent NIS towards perchlorate appear to be similar, the responses of the thyroid hormone levels are very different. For instance, rodent serum T3, T4, and TSH levels were significantly affected by perchlorate in drinking water at doses as low as 0.01 mg/kg-day (14-day exposure) (U.S. EPA, 2002). By contrast, no changes in these hormones were observed in humans exposed to a daily dose of 0.14 or 0.5 mg/kg-day for up to 14 days (Lawrence *et al.*, 2000; Greer *et al.*, 2002). These data support the revised statement "*Healthy adult humans appear to be less sensitive than rats*

to the thyroid-hormone perturbation effect of short-term perchlorate exposures." The PHG is based on a drinking water level that does not inhibit the thyroidal iodide uptake in humans. At the PHG level, there should be neither depletion nor enrichment of the iodide reserve in the thyroid. An uncertainty factor of 10 has been utilized to allow for intraspecies variability.

Comment 6: "The distinction and import of the different mechanisms within the mode of action to dose metrics and integration of diverse data are paramount. The link back to the NIS inhibition is what allows a harmonization of the "noncancer" and "cancer" effects together and supports your assertion that the RfD in this case should supplant the cancer derivation. The sensitivity of the NIS to perchlorate in humans versus rats has not been tested until recently. Given that this is directly related to transient decrements in T4 and T3 that could be associated with neurodevelopmental sequelae, this needs to be considered separately from the upregulated TSH state. Further, it is the regulatory feedback mechanism of decrements in T4 and upregulation of TSH that serves as the basis for monitoring human neonates for hypothyroidism. Humans appear to be about as sensitive if not slightly more sensitive to perchlorate's action at the NIS depending on the chosen dose metric (e.g., peak or area under the curve of perchlorate in the blood). With respect to TSH, the dynamics of the system (the difference in plasma protein binding) in rats suggests that it is more readily tipped into hyperplasia and neoplasia sequelae. Nevertheless the EPA guidance is clear that these tumors are considered relevant to human risk assessment. Tumor development can be considered to be a high-dose phenomenon and a nonlinear process if there is no indication of genotoxicity (as demonstrated in the case of perchlorate)."

Response 6: OEHHA agrees with the above comments, which are consistent with our presumption that preventing inhibition of iodide uptake by perchlorate (by limiting perchlorate exposure) will be protective of all subsequent adverse effects related to thyroid hormone disruption.

Comment 7: "It would also be worthwhile to distinguish between low-dose competitive inhibition effects versus high-dose "discharge" effects. The competitive inhibition at the NIS is saturable, exhibiting classic Michaelis-Menton kinetics. After that saturation, perchlorate concentrations then increase in the blood and passively diffuse down its concentration gradient into the thyroid. The "discharge" seen at high doses is thought to possibly be a combination of both effects and due to the electrochemical charge balance within the follicle (Wolff, 1998)."

Response 7: There are limited data on the "discharge" effect of perchlorate. The exact mechanism of this effect is not clear. However, OEHHA agrees with the commenter that this effect is also of concern.

Comment 8: "Given these differences, more discussion could be devoted to the limitations of ecological epidemiological studies and human clinical studies in capturing the critical course of events, especially with respect to transient decrements in T4 and T3.

Measurements of neurodevelopment, such as decrements in the IQ of a population, must rigorously account for confounding and employ large numbers. These types of investigations for perchlorate-induced hypothyroidism do not exist. While an iodide deficient status may be one aspect of susceptibility, iodine excretion is an indirect surrogate at best for thyroid hormone status. The definition of and best way to characterize hypothyroidism is controversial (see below). The PHG document would aid understanding of the various endpoints and disease "markers" if it described the key events along the pathogenesis and explained how mechanistic studies in rodents and the human data can be mutually informative."

Response 8: OEHHA agrees that the epidemiological data have severe limitations. Not all of the steps in the perchlorate toxicity pathway have been demonstrated in humans, and for this, we agree, the animal data substantiates the chain of potential events. A discussion of the limitations of ecological studies has been added to the final document. Levels of iodine in urine are generally accepted as a measure of the iodine status of a population (NAS, 2001). The U.S. EPA summaries of the animal data and evaluations have been utilized when appropriate.

Comment 9: "Without a mode of action framework, statements such as that on Page 82, *Changes in serum TSH, T3 and T4 levels observed in rodents are judged to be not suitable for this purpose [identification of NOAEL or LOAEL for thyroid tumors]* could argue against the use of any toxicity data in rodents since both neurodevelopmental and thyroid tumor effects are the result of the same NIS inhibition with subsequent perturbations in thyroid hormone economy."

Response 9: The original text was used for arguing against the use of rodent serum TSH, T3, and T4 levels as a basis of quantitative dose-response evaluation. The statement was not against the use of toxicity data in rodents; subsequent revisions may make this clearer.

Comment 10: "[T]he 1998 ERD showed convincing correlations between decrements in T4 and T3 or increases in TSH with hyperplasia and follicular lumen volume. The differences described for "mild" iodide deficiency described on Page 82 can be attributed to the lack of the experimental designs to capture the temporal aspects. As observed in time course experiments, TSH is likely initially decreased because this represents mobilization and depletion of colloid stores. Once colloid is depleted then TSH is upregulated."

Response 10: This is a good observation; no changes to the document seemed necessary.

Comment 11: "Concerns expressed about the effect of the environment (handling, temperature, etc) are overstated. These are addressed in experimental design through the use of control groups and with statistical evaluations such as analysis of variance (ANOVA)."

Response 11: Environmental effects, including dietary and seasonal differences, may complicate comparison of results generated by different laboratories. Discussion of animal toxicity data has been modified in the final document.

Comment 12: "The detailed discussion of iodine deficiency is a particularly useful contribution to the document on perchlorate. However, we feel that it is important not to consider perchlorate toxicity as equivalent to iodine deficiency. It would be helpful for the uninitiated reader, if the strengths and weaknesses of the historical and clinical studies found in the iodide deficiency database were discussed more explicitly to add substance to consideration of individuals with iodine intake below recommendations as a population that could be sensitive to the effects of perchlorate. We also recommend that the authors to read the Iodine Chapter from National Academy of Sciences Dietary Reference Intake volume on trace mineral nutrients issued in January 2001 to update the information provided on nutritional needs for iodine and the status of the population with regard to iodine. The new iodide dietary guidelines for iodine (see Table provided on next page) are different from those cited from Delange (1994) in this report."

Response 12: As reduction of thyroidal iodide uptake is the first step that may lead to the anti-thyroid effects of perchlorate, it is reasonable to assume that many health effects associated with iodine deficiency and thyroid hormone disruption can also be caused by perchlorate exposure. This theory is supported by observations such as: changes in serum T3, T4 and TSH levels, depletion of colloid in the thyroid, and thyroid enlargement, as well as hypertrophy and hyperplasia of thyroid follicular cells in rodents. Most of the final peer reviewers also agreed with OEHHA on this issue.

The new NAS dietary allowances have been cited in the revised PHG document.

Comment 13: "The higher NAS RDAs may suggest a need to rethink aspects of the discussion of the status of the population regarding iodine. The NAS report indicates that less than 25 % of the total population was below the EAR for iodide, but there is a need to look levels of adequacy for susceptible age groups and status during pregnancy and lactation. The NAS also cautions against using urinary iodine as a biomarker for iodine status unless the data are from 24-hour collections or normalized against creatinine. The link of iodine excretion rates to thyroid hormone status is more tenuous."

Response 13: The age- and sex-specific iodine status data of the U.S. population are provided by the NHANES III survey and are discussed in the PHG document. Due to large temporal fluctuation in iodine intake, spot urine samples and 24-hr urine samples are not suitable for characterizing the tails of the population distribution of iodine status. When the sampling is done appropriately, urinary iodide data can provide acceptable estimates of the mean and median of the distribution.

The validity of using urinary iodide measurement as an indicator of iodide status of a population has been confirmed by the scientific and medical communities (see Hollowell *et al.*, 1998).

Comment 14: "We believe that risk characterization discussion in this report would profit from a focused discussion about populations that could be sensitive to the adverse effects of perchlorate because of congenital thyroid problems, in addition to those that suffer from iodine deficiencies. Data that were collected from the National Health Interview Survey by the Office of Water indicate that there are about 4.5 million persons with thyroid disorders in the United States. Women outnumbered men by about 5:1."

Response 14: The final PHG identifies individuals with hypothyroidism, infants, lactating women, pregnant women with less than optimal iodide intake, and their fetuses as sensitive sub-populations. The relationship between thyroid illnesses and dietary iodide intake is complex, and hypothyroidism is a subset of all the thyroid disorders. We hope that the extensive revisions will provide a more straightforward discussion of these factors.

Comment 15: "There are a number of deficiencies of the Lawrence *et al.* (2000) study that were either not noted or not elaborated upon in the PHG document. These include: the small sample size, that the subjects were males of "normal" thyroid status versus the target susceptible population of pregnant female with hypothyroidism, the resolution of the RAIU measure, and that the subjects were not instructed to drink the perchlorate at specified times so that sample times were not consistent with respect to key events of thyroid hormone disruption. ... Due to the rapid elimination of perchlorate, serum concentrations fluctuate significantly with dosing schedule and this was not controlled in the experiment."

Response 15: The study reported by Lawrence *et al.* (2000) suffered from a number of limitations such as small sample size, only male subjects, and relatively high dietary iodide intake. All these limitations have been discussed in the risk assessment. Some of the deficiencies in the available human data have been overcome by the results reported by Greer *et al.* (2002). While the study results of Lawrence *et al.* (2000; 2001) and Greer *et al.* (2002) are mutually supportive, the PHG is now based on the thyroidal iodide uptake data reported by Greer *et al.* (2002).

Comment 16: "Another critical concern regarding the use of the Lawrence *et al.* (2000) data as the basis for the derivation is the use of the average across three sample times and a single point to establish a dose-response. Given the temporal aspects discussed above, we question the justification to average the three sample time points. Perhaps the rationale is that because a controlled time course was not provided then the average is all that can be used, but this should be clarified. It may set a dangerous precedent when trying to utilize data from other studies that have a better handle on when the perchlorate was ingested."

Response 16: The final PHG is now based on the human data reported by Greer *et al.* (2002). Also, as shown by Greer *et al.* (2002), there is a strong correlation between the 8-hr and 24-hr RAIU measurements

Comment 17: "No obvious criterion is established to designate the adversity. To be explicit, 50% iodide inhibition in one study (Stanbury and Wyngaarden, 1952) and now 38% (Lawrence *et al.*, 2000) has been identified as a LOAEL. It is also not clear from Table 27 how the average percent decrement across the three time points can be 38% when the greatest reported value is 23.6 ± 2.6%."

Response 17: In a given study, the lowest dose that resulted in a significant inhibition of thyroidal iodide uptake is identified as the LOAEL. For the PHG program, OEHHA uses the terms LOAEL and NOAEL without an explicit definition of "adverse;" severity of effect can be considered in choices of uncertainty factors. The degrees of inhibition associated with various LOAELs are often not the same, since this is defined by dose choices in the studies. However, the point of departure for the PHG is now based on a benchmark dose calculation derived from the *Greer et al.* (2002) study, providing a clear set of criteria.

Comment 18: "The abstract of Greer *et al.* (2001) is used to justify a dose-response but reliance on an abstract for this critical aspect is troublesome, especially given the concerns regarding QA/QC noted above. We note another abstract (letter to the editor) could be included that suggests that 3 mg is a NOAEL (Lawrence *et al.*, 2001). In order to support the use of these limited human data for the point of departure in the risk derivation, the PHG document must be more explicit on how it is arriving at a dose-response "function" by bootstrapping these studies together."

Response 18: We were reluctant to use data from a non-peer reviewed abstract as the basis for our PHG. However, the Greer study has now been published (Greer *et al.*, 2002). The results are the primary basis of the final PHG. An uncertainty factor was used for the extrapolation of data obtained in healthy, euthyroid adults to infants and pregnant women of low thyroid status.

Comment 19: "We are not convinced...that the degree of iodide inhibition observed in the Stanbury and Wyngaarden (1952) study or these abstracts [noted in comment 18] on new lower dose studies should represent NOAEL levels when considered in light of study design deficiencies, power of resolution, and concern for transient decrements in T4 to cause neurodevelopmental damage. Using these data in this way may engender critical comment with respect to the definition of adversity and the adequacy of the uncertainty factor (UF) for intrahuman variability. ... We strongly recommend a more rigorous review of the two abstracts (perhaps wait for peer review of studies) and some serious thought about a criterion for the degree of iodide inhibition when designating a LOAEL or NOAEL. The traditional intrahuman UF is an empirical factor that is motivated on data from the 1950's that did not include effects at levels of observation (unit of analysis) much below the organ or tissue level, and did not include endocrine disruption. An additional modifying factor (MF) could be considered for the design deficiencies of the chosen studies to help offset their inadequacy to define a LOAEL/NOAEL based on the mode of action and of the intrahuman UF to address susceptible populations. A UF for data base deficiencies might be warranted based on the concern for other endpoints such as immunotoxicity and the issue of in utero programming or lack of chronic data."

Response 19: The peer review and acceptance for publication of the most recent human study (Greer *et al.*, 2002) addresses part of the above comment. We acknowledge that extrapolation of subacute inhibition of thyroidal iodine uptake in humans to potential mental retardation of developing fetuses is a major quantitative unknown in the risk assessment. However, OEHHA believes that preventing NIS inhibition will likely prevent all such neurodevelopmental sequelae, and that an uncertainty factor of 10 is appropriate to account for the inter-individual variability. With the availability of animal and human toxicity data, several peer reviewers suggested that an additional uncertainty factor for immunotoxicity or in utero programming or lack of chronic data is not warranted. We agree.

Comment 20: "We do agree with the use of the adult consumption values to convert the RfD to a PHG equivalent level when considering a neurodevelopmental effect of in utero exposures. The text on Page 85 says 70 kg is used whereas the formula uses 65 kg. We are not aware of a citation source recommending a value of 65 kg for pregnant women."

Response 20: This section has been revised.

Comment 21: "Comments on caveats with respect to the use of a relative source contribution of 40% include those below with respect to the quality of the data on indirect exposures. Recent guidance from the Office of Water (US EPA, 2000) on the methodology for Deriving Ambient Water Quality Criteria provides a decision flow chart for derivation of the RSC and recommends 80% as a ceiling and 20% as the floor for this factor (see Chapter 4, section 4.2.2.4 on apportionment decisions). EPA does not recommend the high-end intakes be subtracted for every exposure source since the combination may not be representative of any actually exposed population or individual. The PHG document would benefit from a more detailed explanation of the quantitative support for the use of 40% as the RSC."

Response 21: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al.*, 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types.

Comment 22: "The thyroid tumors occurred in the F1 male pups at the high dose (30 mg/kg-day) of the 2-generation reproductive study. The fact that these tumors occurred at week 19 in the F1 pups suggests a potential for in utero programming, given the statistical significance of the 19 week data in light of the NTP 2-year bioassay data for all chemicals to date that have caused similar tumors. An additional uncertainty factor for in utero programming / lack of studies of addressing this duration could be considered for this finding. Using a non-linear approach, the 30 mg/kg-day would be a LOAEL and the 3 a NOAEL in this study for tumors. A full factor of 10 applied to the NOAEL would result in an estimate of 0.3 mg/kg-day. This is consistent with the NOAEL for hyperplasia in the study at 3 and the NOAEL for hypertrophy at 0.3 mg/kg-day in the F1 pups. The PHG document does not provide a rationale for the choice of hypertrophy alone in the F2 generation pups at 0.3 mg/kg-day, nor for how the concern regarding in utero programming was addressed. There is also no rationale provided for the reduced factor of 3 for interspecies extrapolation."

Response 22: The discussion of animal toxicity data has been revised in the final PHG. Hypertrophy and hyperplasia of the thyroid are no longer considered as potential critical endpoints in the PHG document, because we are focusing on the human endpoints. A BMDL of 0.0037 mg/kg-day for inhibition of iodine uptake by perchlorate was identified by benchmark dose modeling of the human data; this value is 75 times lower than the NOAEL of 0.3 mg/kg-day derived from the 2-generation reproductive study described above.

Comment 23: "In order to avoid exacerbating the potential for misinterpretation of data noted in the previous section, the PHG document should be consistent across studies in its critique of experimental design, particularly with respect to discussions of the impact of design on observed results and of the strengths of various studies for drawing inferences."

Response 23: The section on animal toxicity being referred to in this comment has been re-written with a more consistent discussion of studies, including many new studies recently made available by U.S. EPA.

Comment 24: "[T]he definition and detection of hypothyroidism is a very controversial topic at this time and new data are emerging rapidly. Additional discussion devoted to this topic per se would help to avoid confusion. We discourage discounting the relevance of thyroid hormones from any species in that context. A more critical view of the limitation of the human data is required on this topic as well (e.g., see Meier *et al.*, 2001)."

Response 24: Hypothyroidism is generally defined as having low serum T4 and high serum TSH. A detailed discussion of the clinical symptomatology is beyond the intended scope of the PHG document.

There are significant and important quantitative differences in the sensitivity across species of the thyroid hormone balance towards the anti-thyroid effects of perchlorate.

Though the sensitivities of human and rodent NIS towards perchlorate appear to be similar, the responses of the thyroid hormone levels are very different. For instance, rodent serum T3, T4, and TSH levels were significantly affected by perchlorate in drinking water at doses as low as 0.01 mg/kg-day (14-day exposure) (U.S. EPA, 2002). By contrast, no changes in these hormones were observed in humans exposed to a daily dose of 0.14 or 0.5 mg/kg-day for up to 14 days (Lawrence *et al.*, 2000; Greer *et al.*, 2002). Our decision to base the PHG on the human effect level (informed by the rodent mechanistic data, but not driven by the rodent effect levels) avoids the complexity of attempting quantitative cross-species extrapolations from the available data.

Comment 25: "We were very confused with respect to presentation and attribution regarding statistical analyses. In many instances the document uses the original study reported results (e.g., Argus Laboratories, Inc.) versus re-analyses by the EPA interchangeably when discussing results in the text. This is particularly true with respect to the thyroid hormone analyses. The one set of tables (6a and 6b on Page 16 that present the Caldwell *et al.*, 1985 study) where it is apparent that results are from EPA statistical analyses, the footnote does not describe the statistics correctly yet these are clearly presented in lines 1 through 10 on Page 5-9 of the EPA document. It is important to appreciate that these re-analyses represented correction of misapplied statistics on behalf of the contract labs and in some cases, corrections with respect to animal identity (e.g., Crofton, 1998b). EPA typically applied step-down analysis of variance (ANOVA), accounting (when necessary as indicated by significant interactions) for gender and treatment as independent, between-subject variables with correction for multiple comparisons whereas the contract labs were typically applying a series of individual ANOVA tests without accounting for interaction or correction for multiple comparisons [e.g., in the 90-day Springborn study where the contract lab did this across gender, treatment and time (different sac days of 14, 90 or 120)]."

Response 25: The section on animal toxicity has been re-written. Some of the U.S. EPA results and conclusions are included, when appropriate.

Comment 26: "The PHG document was correct in its use of the Wolf (2000) report for the evaluation of the thyroid histopathology, but the statistical analysis procedure for the data is not presented in the text. From footnotes in some tables it appears that Fisher exact tests may have been performed for each study but it is not stated if correction for multiple comparisons was applied and in some table the p value is 0.05 whereas in others it is 0.01. It is unclear why a benchmark dose analysis was not attempted to better account for the influence of dose spacing and dose levels. Further, the rationale for not combining the male and female data is not presented."

Response 26: The section on animal toxicity has been re-written, and the above points are no longer applicable. We have developed a benchmark dose approach to evaluate the human data reported by Greer *et al*. (2002).

Comment 27: "The PHG document would appear more balanced if it presented critique of experimental design attributes for all studies, especially with respect to the human ecological epidemiology and cross-sectional occupational studies. The PHG document seemed to only critique attributes of the Brechner *et al.* (2000) study. Certainly all of the studies suffer from lack of quantitative exposure data. In light of the controversies with respect to the utility of T4 versus TSH in screening, the detractions of the Brechner *et al.* (2000) study presented in the PHG document should be reevaluated."

Response 27: In the revised document the limitation of using T4 as a screening tool for the measurement of TSH is discussed regarding a number of ecological studies, in addition to the one reported by the Brechner *et al.* (2000). Due to the difference in proportion of blood samples taken in the first two days of life between the two cities in the study of Brechner *et al.*, OEHHA believes the reported results may be too affected by sampling bias to be relied upon. The final PHG document has been revised to indicate this problem existed in other studies (Schwartz, 2001; Li *et al.*, 2000) as well.

Comment 28: "We note that Schwartz (2001) is an important ecological epidemiology study performed in California as a Master's Thesis at the University of California at Berkeley with support by the California Department of Health Services, that shows an association of perchlorate exposure with decrements in T4 observed in California neonates. This study could be added to strengthen the analyses of the available human data."

Response 28: We agree that this study provides relevant additional perspective, and a discussion of it is now added to the PHG document.

Comment 29: "[S]eparation of the toxicokinetic versus toxicodynamic considerations with respect to perchlorate would be worthwhile to distinguish. Since the document invokes iodide deficiency in the effects section, ADME of iodide per se should also be presented as well as the competitive inhibition effects of perchlorate on iodide ADME."

Response 29: OEHHA believes detailed discussion of absorption, distribution, metabolism and excretion of iodide is outside the scope of the PHG document. Mutual inhibition effects of perchlorate and iodide on the NIS are discussed.

Comment 30: "We would have expected the ADME section in the document to report on key data evaluated in the 1998 ERD (e.g., Chow *et al.*, 1969; 1970; Channel, 1998c; Fisher, 1998a). This section would also be greatly informed by new PBPK models and data that were presented as posters at the 2001 Society of Toxicology meeting (Clewell *et al.*, 2001; Fisher *et al.*, 2001; Mahle, *et al.*, 2001; Merrill *et al.*, 2001; and Yu *et al.*, 2001)."

Response 30: Additional information is added to the PHG document from several of these sources. For details on animal toxicity data and PBPK modeling, we cite and refer to the U.S. EPA risk assessment on perchlorate.

Comment 31: "Descriptions of ADME are difficult to evaluate when descriptions of studies do not provide the dosage (e.g., top of page 13). Quantitative mass balance also helps to interpret the findings and should be provided where available (e.g., page 13 under "metabolism")."

Response 31: Dosage information is provided when available.

Comment 32: "The second paragraph on Page 88 is inaccurate. Any tissue with NIS (e.g., thyroid, skin, GI, and breast) has the potential to have a higher steady-state concentration than the blood but this is not the same as "accumulation." We also note that the table on includes a number of divalent or trivalent cations yet the text on page 6 restricts salt formation to monovalent cations."

Response 32: The final document has been revised to address these points.

Comment 33: "To aid the readers in appreciating the route-specific nature of the data base, the limitations with respect to the data on the inhalation route of exposure should be discussed in greater detail. The description that perchlorate can be inhaled does not provide critical evaluation. The occupational studies quoted did a poor job of characterizing particle size and distribution and its effects on deposition as discussed in the 1998 ERD. It is misleading to use the blood and urinary excretion levels as reported in the original papers without proper evaluation of the inhalation dosimetry (e.g., Pages 9, 11 and 56). Note also that the 1998 ERD discusses that the stakeholder concern for inhaling contaminated shower droplets is mitigated by the facts that the vapor pressure prevents it from coming out of solution and that shower droplet size range from 200 to 3,000 μm, i.e., not inhaleable."

Response 33: There are limited data on the availability of nonvolatile chemicals in shower droplets. However, we agree that the relative exposure by inhalation is so small that it should be negligible. It is not clear to us why the commenter said it is misleading to use blood and urinary excretion levels as indicators of perchlorate exposure, because these levels reflect the systemic dose and include all routes of exposure.

Comment 34: "There are a number of areas in the document where we would recommend careful clarification of the status of the EPA assessment effort."

Response 34: We have acknowledged that the U.S. EPA (2002) perchlorate risk assessment is a draft. However, extensive discussion of the U.S. EPA's process is outside the scope of our PHG documents, and is best left to U.S. EPA.

Comment 35: "Page 32 of the document [states] *"Because of statistical problems stemming from extreme variability in the data, U.S. EPA did not attempt to establish a LOAEL or NOAEL for these effects (U.S. EPA, 1998a)"*. This is incorrect. The EPA clearly states in the beginning of Section 5.2.3.4 of the 1998 ERD document that EPA disagreed with Argus Research Laboratories, Inc. that no perchlorate-induced changes

were detected in motor activity on PND14. EPA unequivocally asserts that the effects, despite the variability and inadequate statistical analyses, should be "considered biologically significant until additional data can be marshaled to suggest or prove otherwise" at the end of that section. The Crofton *et al.* (1998) memo cited in the document provides additional details on the EPA position. These finding were the basis for an additional (repeat) motor activity study in rats performed by the United States Navy in 2000."

Response 35: The animal toxicity section has been revised, and the quoted statement is no longer included.

Comment 36: "The PHG document is again unclear with respect to the brain morphometry results, and inconsistent with respect to presenting results of the Argus Laboratories Inc. report versus re-analysis by EPA scientists. The percent change in the corpus callosum presented in the document represent the Argus results whereas the effect level designations cited represent conclusions by EPA based on preliminary re-analysis once again using different statistical techniques. The results for the hippocampal gyrus and caudate putamen that the PHG document reports are then once again the Argus analyses that had noted deficiencies. At the peer review, concern was expressed for the variability and plane of cut for these morphometry measurements in the Argus study. It was recommended that the original slides and remaining blocks be evaluated to see if additional morphometry could be performed. In the case of the former it was determined that the slides were too variable for accurate measurements and for the latter that the blocks were too small to reface in order to achieve adequate sections. A new study to repeat the evaluation of effects on brain morphometry was also recommended and results recently obtained this summer."

Response 36: The animal toxicity section has been revised to clarify which report is being described, and whether the interpretation of results is that of Argus, U.S. EPA, or OEHHA.

Comment 37: "EPA conclusions that were supported by the external peer review on another key endpoint, immunotoxicity, are also not reported. Here again the discrepancy between the contractor analyses and the EPA analyses are important — the PHG document merely provides text and table from the contract report. If there is a rationale for not agreeing with the different approaches taken by EPA for analysis of the data, then it should be clearly presented. Rather than concluding that the data were too variable, EPA instead chose to highlight the trends and suggest that a picture might emerge if additional assays were conducted. In particular, the phagocytic index for the macrophages is a more typical assay used to evaluate this functional capacity and was recommended for future study due to the trends in the data. Further, the sheep red blood cell (SRBC) plaque assay, an assay required in test rules that has been shown to be predictive for immunosuppression and the only assay that would evaluate humoral immunity, was requested in the ERD. The external peer review panel agreed with the analysis presented by the EPA immunotoxicologist (Smialowicz, 1999) that the performance of this test was inadequate and a repeat set of SRBC assays was

recommended. The external peer review panel also recommended that a test of sensitization be performed per EPA request in the 1998 ERD. The concern for potential immunotoxicity from perchlorate is clear in the EPA ERD, the additional analyses presented at the peer review, and in the recommendations from the peer review panel. EPA retained a UF for database due in part for this concern. Evaluation of the new data from the recommended studies should be incorporated before more definitive statements can be made on immunotoxicity."

Response 37: The animal toxicity section has been revised, but OEHHA does not attempt to re-interpret these immunotoxicity data.

Comment 38: "While the PHG document notes concern for plant uptake of perchlorate contributing to exposure sources in addition to drinking water, the document is silent on the issue of perchlorate in fertilizer. The citations quoted to suggest the concern for plant uptake in fact plant and home garden type fertilizers that were not typical of agricultural applications and which lacked rigor with respect to sample chain of custody and handling (riffling and representative sample preparation). Because of considerable concern provoked by these initial studies, a rigorous analysis with chain of custody and state-of-the-art sample preparation was undertaken by the National Risk Management Research Laboratory (NRMRL) in ORD in partnership with The Fertilizer Institute. The report has recently been released and results indicate that there is no concern for perchlorate in fertilizer with the exception of that containing Chilean caliche (U.S. EPA, 2001a,b). We are aware, through personal communications, that manufacturers that rely on Chilean caliche have changed their formulation process to remove perchlorate."

Response 38: A discussion on the concern about fertilizer contamination and the work done by U.S. EPA has been added to the PHG document.

Comment 39: "It should also be noted that the studies to date with respect to plant uptake are preliminary. Definitive mass-balance studies representative of crop growing cycles have not been performed. A protocol for a "farm gate" study to sample various types of crops and food commodities (e.g., grain versus leaf versus root, milk, citrus) at main distribution centers has been developed with the help of the USDA and FDA but has not to date been funded by the DoD. Studies of biotransport (sampling for perchlorate in various sediments, soils, plants and animal receptors) at six contaminated DoD sites also suggest a potential for indirect exposure sources but again are not definitive. One of the major challenges to overcome has been the development and validation of analytical methods used to detect perchlorate in sediments, soils, plants and animal species. Preliminary data from the National Exposure Research Laboratory (NERL) of the ORD suggest that absorption is a function of soil type, pH, and temperature (Susarla *et al.*, 2000). We are not aware of citations to support the statements regarding the lack of absorption to soil particles and mechanisms for accumulation of perchlorate in soil on Page 9."

Response 39: The discussion on page 9 has been revised; it now discusses later studies that have provided more information on perchlorate in the environment, especially in foods.

Comment 40: "Another public concern is whether water is being monitored for the occurrence of perchlorate so we also recommend that it be noted what sampling strategies are underway by Cal DHS and EPA. With respect to the latter, Perchlorate was placed on the Unregulated Contaminants Monitoring Rule (UCMR) in 1999 (Federal Register, 1999) and monitoring began in January 2000. It would also be worthwhile to note that EPA Method 314.0 (Federal Register, 2000) now exists for analysis of perchlorate in water on Page 9, second paragraph under "Water"."

Response 40: The new information is added to the PHG document.

Comment 41: "Establishing the lack of genotoxicity was pivotal in establishing the mode of action for tumor formation by perchlorate to be its anti-thyroid hormone effect via NIS inhibition per the EPA thyroid tumor assessment guidance (U.S. EPA, 1998b). Because concern for this endpoint is likely to be great, and the anti-thyroid effect serves as the basis for invoking a nonlinear extrapolation and the platform for the harmonization of the "noncancer" and "cancer" approaches in both assessments, it should be noted in the final sentence of this section on Page 31 that the external peer reviewers agreed with the EPA and the NIEHS conclusions regarding the lack of genotoxicity of perchlorate and its likely mode of action."

Response 41: OEHHA agrees with the commenter that the negative genotoxicity data set is important in choosing a nonlinear method for the evaluation of the rodent thyroid tumor data. The discussion has been slightly revised, but we have not specifically cited the opinion of our first peer reviewers in the document, preferring published sources wherever possible. Extensive discussion of the U.S. EPA's risk assessment is outside the scope of our PHG documents.

Comment 42: "The text for this section on Page 25 begins "A two-generation reproductive study in rats had been conducted by Argus Research Laboratories (1998b),["] and this suggests that the study was completed at that time. In order to help the readers through the time line issues with these data, it would be useful if the document clarified that only preliminary data were available in 1998 and the completed study not published until 1999. It is not noted until Page 39 that the study results reported are incomplete. The preliminary analyses presented by EPA at the peer review (Clegg, 1999) evaluated effects on reproductive measure. The tumors observed in the F1 high-dose males were a new finding in the later PWG thyroid effects evaluation. We note that you cite some of the 1999 preliminary analysis memos that were presented at the peer review (e.g., regarding brain morphometry: Geller to Jarabek, January 27) but in this case do not include the reproductive endpoint citations. We will be happy to provide those if required. Also, it should be noted that we cite those internal memos as publications of the principal author of the memo (e.g., Geller, 1999). It would also be

worthwhile to more clearly note at the very beginning of the section that preliminary analyses presented at the 1999 peer review and in the 1998 ERD assessment evaluated all data (reproductive endpoints plus satellite thyroid histopathology and hormones) through the F1 generation and that only the final thyroid histopathology data (as summarized in the Wolf, 2000 memo online) are currently available for critical evaluation. Evaluation of reproductive toxicity per guidelines requires the final report on both generations (F1 and F2)."

Response 42: The section on animal toxicity has been extensively revised, and more details on this study and interpretations of the data have been provided.

Comment 43: "The Argus 1998 development study in rabbits did demonstrate a perturbation of thyroid hormone economy in the dams. Further, as discussed in the EPA 1998 ERD, on Page 5-42, the EPA was concerned about fetal malformations that were observed on gross external examination in the pilot range-finding study and that was the reason for an expanded dose range used in the definitive study. The assertion on Page 40 that the rabbit is not an appropriate model for developmental toxicity because of differences in placental iodide transport presumes that the inhibitory effects of perchlorate on the NIS are equisensitive to those in the rat. However, the sensitivity of the NIS in rabbits has not been evaluated and the studies cited for the placental iodide transfer are dated at best. The more salient feature of the study is that the thyroid and brains were not evaluated in the pups, thus precluding species comparison of the definitive endpoints linked to the mode of action. While we are now appreciating that characterization of the hypothalamic-pituitary-thyroid feedback axis and the dynamic state of thyroid hormone economy is temporally complicated, even in the rat. Characterization has only just begun in other species. It may be better to remark on the remarkable similarity on in the effect of perchlorate on thyroid hormone across species, noting these developmental studies in rabbits and the immunotoxicity studies performed in mice as mutually corroborative that this important feedback is conserved in all species. The objective of the developmental study in rabbits was to meet requirements for conducting studies in two different species. This study does meet that objective with respect to general maternal and gross developmental effects and could be so characterized but with the above caveat for the refined definitive endpoints. The inadequacy of the rabbit model was what motivated the external peer review to recommend a development (Segment II) study in rats. This recommendation was also carried out."

Response 43: The similarity in the anti-thyroid mechanism of perchlorate across animal species is indeed remarkable. Nevertheless, the fact that placental iodide transfer in humans is different from that of rabbits weakens confidence in the negative reproductive and developmental toxicity results observed in the study.

Comment 44: "[T]he Argus laboratory does not use the convention for post-natal day designation as typically used and recommended in the EPA testing guidelines for developmental neurotoxicity (US EPA, 1998c). Rather than designate the day of birth as PND0, Argus uses the day of birth as PND1. Thus, data reported as PND12 are really PND11 per accepted nomenclature. This is an important fact for evaluating

neurodevelopmental sequelae because reviewers may be assuming the convention with respect to evaluating landmark behaviors and morphometry. The document is not consistent with respect to "postpartum" versus "postnatal" day in texts and tables. Given the wide audience for this assessment, we recommend choosing the latter and sticking with it."

Response 44: More detail has been provided on this study in the section on animal toxicity, with more consistent descriptions.

Comment 45: *Regarding the Pathology Working Group Report and thyroid re-analysis:* "The PHG document needs to clarify that colloid depletion was a parameter recommended for review in all the studies, not just the developmental neurotoxicity. It is a sensitive parameter per the mode of action, i.e., colloid depletion precedes decrement in thyroid hormone, so it is not clear why the measure was not reported upon in the PHG document. Both the PWG report (EPL, 2001) and the Wolf (2000) memo should be cited and the URL for these reports would be useful as well: http://www.epa.gov/ncea/perch.htm."

Response 45: The section on animal toxicity has been revised, but OEHHA has not chosen to describe the various endpoints to the level of detail recommended by U.S. EPA, since the studies do not form the basis of our risk assessment.

Comments from University of Massachusetts

Comment 1: "Generally, the review is thorough and accurate. The logic underlying the choice of the study by Lawrence *et al.* (1) is clear and justifiable. The calculation of the PHG is clear and defensible."

Response 1: No changes needed.

Comment 2: *However,* "a critical element of perchlorate transport in humans was omitted in this review and it is the opinion of this reviewer that it should be thoroughly reviewed and considered in the calculation of the PHG. Specifically, the transport mechanism that "traps" iodide in thyroid is also present in lactating breast, in placenta, and in neonatal gut epithelium. This is important because, for example, iodide in breast milk is concentrated 20- to 50-fold over that of maternal serum. This effect is mediated by the sodium-iodide symporter and is blocked by perchlorate. There is every reason to believe that perchlorate also is concentrated in milk, but measurements of perchlorate in milk have not been reported. Thus, the proposed PHG does not factor in the known deleterious effects of perchlorate on the ability of an infant to concentrate iodide, and does not consider the possibility that perchlorate is actually concentrated by several-fold (20- to 50-fold?) in breast milk."

Response 2: OEHHA agrees with the commenter and is concerned about the exposure of infants to perchlorate through the breast milk. However, very little information on the

secretion of perchlorate into human breast milk is available at this time. Kirk *et al.* (2003) reported the detection of perchlorate at 3-4.5 µg/L in a single breast milk sample and between 1.7 to 6.4 µg/L in seven supermarket dairy milk samples. As the extent of exposure of the mother and the cows are not known, it is not possible to estimate the bioconcentration factor for perchlorate in milk. The researchers did analyze local tap water and found perchlorate levels ranged from below the limit of detection (0.5 µg/L) to above 4 µg/L, with a mean value of 2.5±1.1 µg/L in the samples in which it exists above the limit of detection.

In a recent animal study, Yu *et al.* (2001) dosed female rats in the 0.01 to 10 mg/kg-day range and showed that the concentration of perchlorate in their milk was about twice as high as that measured in the serum of the dams. It is also interesting to note that in the physiologically based pharmacokinetic modeling results in rats reported by Clewell *et al*. (2003), they estimated that pups drinking their mother's milk receive a greater perchlorate dose than the dam, on a mg/kg basis (up to seven-fold greater at the lowest perchlorate dose in their study). They also estimated that serum perchlorate levels (expressed as area under the curve) in neonatal rats drinking their mother's milk (after exposure of the mothers to perchlorate in their drinking water) are slightly lower than those of male rats, pregnant rats, and lactating rats, which presumably reflects an enhanced excretion rate, counterbalancing the enhanced intake rate in the neonate.

It should be noted the PHG is set at a level that is not likely to inhibit uptake of iodide into the thyroid. Assuming the properties of NIS in the thyroid are similar to those in the mammary gland and the placenta, individuals exposed to perchlorate at the PHG level are not likely to have iodide transport inhibition in these two tissues.

Comment 3: "The discussion on page 14 about the two forms of cretinism may be confusing. Specifically, the document reads in part, "People with neurologic cretinism have mental and neurologic abnormalities but appear euthyroid; those with myxedematous cretinism, in contrast, have hypothyroidism." Although unintended, it reads as though the point is to suggest that myxedematous cretinism is not associated with neurological dysfunction, only hypothyroidism. Later in the document, this issue is again addressed. However, it loosely implies that the neurological deficits associated with the two forms of cretinism are the same. In fact, they are different and this might be clarified for the sake of accuracy."

Response 3: This section has been rewritten to address the comment.

Comment 4. *The proportion of children with goiter in all groups in the Crump et al. study is very high, and represents an unexplained, confounding variable.*

Response 4: A note has been added to the discussion of the study reported by Crump *et al.* (2000) to indicate that this is a confounding factor.

Comment 5: "The study by Lamm and Doemland (11) reports that the incidence of congenital hypothyroidism (CH) recorded in seven counties is not correlated with the

level of perchlorate contamination in those counties. However, the authors do not point out that, by far, the major cause of CH is neonatal thyroid dysfunction including thyroid dysgenesis and agenesis (12-14). Moreover, among children with CH, those with T4 levels at birth below a specific threshold exhibit neurological deficiencies despite early T4 therapy (15). Thus, it is predictable that the incidence of CH would not be altered by perchlorate given the size of the populations reported. However, it would be more important to examine T4 and TSH levels among those children exhibiting CH."

Response 5: This is a good point, but seemed less germane for the purpose of our discussion in the PHG; no changes made.

Comment 6: "It appears that the OEHHA document incorrectly faults the Brechner *et al*. paper on one specific issue. Specifically, the statement on page 50 of the OEHHA document that, "In fact, Brechner *et al.* (2000) noted in the paper that TSH levels measured in Yuma were not significantly higher than those measured in Flagstaff when days since birth and race/ethnicity were controlled for." appears to be incorrect. Brechner *et al.* (2000) state that, "Also of interest is the fact that neonatal T4 values did not differ between Yuma and Flagstaff after adjusting for race/ethnicity (data not shown)." It is not clear what Brechner *et al.* meant by this statement (all T4 levels or just those that triggered the TSH assay?). But, it clearly does not mean that TSH levels are not different after the adjustment."

Response 6: OEHHA believes the authors meant all T4 levels. Brechner *et al.* showed that TSH levels of the two cities were different after adjusting for race/ethnicity and age at the time of sampling. The risk assessment has been revised.

Comment 7: "[T]his reviewer would argue that the weaknesses attributed to the Brechner study are shared to some extent by all of these epidemiological studies. Therefore, the reasoning used to justify eliminating this study from consideration, if applied equally to all of these studies, would be cause for eliminating them all. Specifically, there are no individual measures of perchlorate. Brechner did not have perchlorate measures for the period of study, which seriously weakens the conclusions. However, it is only slightly worse than the study of Li *et al.*, which reports a single measure of "Las Vegas" and "Reno" (per month) without any information about where the mothers came from (e.g., are Las Vegas and Reno regional medical centers?)." ... "However, inasmuch as they all demonstrate that there are no widespread differences in T4 levels of neonates associated geographically with perchlorate contamination, they are useful (with the possible exception of Crump *et al.* in which very high levels of goiter are observed.)."

Response 7: Point noted. The document has been revised to better address the similarities, differences, and methodological weaknesses of the various studies.

Comment 8: "The study by Gibbs *et al.* (18) reports that perchlorate was not a significant predictor of the cross-shift change in any of the thyroid parameters. While this is accurately reported on page 55, it should be noted that given the serum half-life of T4 in humans (nearly 7 days), it would be very unlikely that T4 would exhibit a change in

serum over a single shift. However, the absolute values reported for these shift workers are within the normal range."

Response 8: A note has been added to the discussion of the study by Gibbs (1998) indicating that given the relatively long serum half-life of T4 in humans (5-9 days), it would be very unlikely that T4 would exhibit a change in serum over a single shift.

Comment 9: "Identifying iodide uptake in human studies as the critical end-point for both non-carcinogenic and carcinogenic health effects. This is an important determination and is very well-reasoned and clearly justified in the document. In the absence of specific studies focused on the effects of perchlorate on maternal, fetal and neonatal thyroid function, or thyroid hormone action, it is critical to use this particular end-point to establish a PHG."

Response 9: We agree; no change needed.

Comment 10: "The studies reviewed and those chosen to focus the calculation of the PHG is nearly exhaustive. For completeness, the study of Li *et al.* (19) might be included (it is not reviewed). This study shows that serum TSH is not different in neonates triggered by low T4 in Las Vegas compared to Reno, NV."

Response 10: The study has been added to the PHG.

Comment 11: "Final PHG Calculation. The major issue is how to account for the fact that perchlorate will reduce iodide uptake across the placenta and into breast milk, and will very likely be concentrated in breast milk and perhaps in the fetus. The reduction of iodide in milk by perchlorate is well-known; however, the ability of perchlorate to become concentrated in milk has not been formally documented. Therefore, it would appear important to consider this in the uncertainty factor. Thus, instead of a factor of 10 for inter-individual variability, it would appear important to increase this at least to 20. This would produce a PHG of 3 ppb. However this is done, it appears a major weakness to fail to consider iodide and perchlorate uptake into breast milk, the volume of milk consumed and the body weight of the infant."

Response 11: OEHHA agrees with the commenter and is concerned with the exposure of infants to perchlorate through the breast milk. However, very little information on the secretion of perchlorate into human breast milk is available at this time. Kirk *et al.* (2003) reported the detection of perchlorate at 3-4.5 µg/L in a single breast milk sample and 1.7 to 6.4 µg/L in seven supermarket dairy milk samples. As the extent of exposure of the mother and the cows are not known, it is not possible to estimate the bioconcentration factor for perchlorate in milk. The researchers did analyze local tap water and found perchlorate levels ranged from below the limit of detection (0.5 µg/L) to above 4 µg/L, with a mean value of 2.5±1.1 µg/L in the samples in which it exists above the limit of detection. In a recent animal study, Yu *et al.* (2001) showed that the concentration of perchlorate in rat's milk was about twice as high as that measured in the serum of the dams, while Clewell *et al*. (2003) using PBPK modeling showed that the

doses to neonatal rats drinking this milk could be higher, on a body weight basis, than the dose to the mother. However the serum perchlorate concentration predicted for the neonatal rat is actually lower than that of the pregnant rat, lactating rat, and adult rat. Comparable calculations for humans are not yet available.

It should be noted the PHG is set at a level that is not likely to inhibit uptake of iodide into the thyroid. Assuming the properties of NIS in the thyroid are similar to those in the mammary gland and the placenta, women exposed to perchlorate at the PHG level are also not likely to have iodide transport inhibition in these two tissues.

In the revised document, OEHHA applied a benchmark dose approach to evaluate the human data reported by Greer *et al*. (2002) and developed a BMDL of 0.0037 mg/kg-day. Upon applying a relative source contribution factor of 0.6 and an uncertainty factor of 10, a PHG of 6 ppb was calculated.

Comments on the First Public Release Draft

Comments from U.S. Environmental Protection Agency Office of Research and Development and Office of Water

Comment 1: *U.S. EPA questioned the wisdom of removing the tabular presentation of critical data in the laboratory animal toxicity section.*

Response 1: Animal toxicity studies as well as human studies were evaluated, but the OEHHA risk assessment focuses on the human data. Due to the complexity in interpreting the animal data, OEHHA refers readers to the U.S. EPA (2002) risk assessment for detailed description and analysis of some of the data.

Comment 2: *U.S. EPA suggested that OEHHA should distinguish hypothyroxinemia from hypothyroidism with respect to perturbation of thyroid hormone homeostasis.*

Response 2: The PHG document has been revised to clarify the distinction between hypothyroxinemia and hypothyroidism.

Comment 3: *U.S. EPA disagreed with the statement "rodents are found to be highly sensitive to the anti-thyroid effects of perchlorate...[when compared to humans]" and considers that the assertion that rodents are much less sensitive than humans is unfounded with respect to the neurodevelopmental sequelae. Their position is that the existing data in humans on the effects of perchlorate on thyroid hormones is inadequate to be informative.*

Response 3: In terms of the susceptibility to perturbation of the thyroid hormone homeostasis, experimental data show that healthy adult humans are generally not as sensitive as rodents to short-term perchlorate exposures. However, the statement in question has been revised. The most likely mechanism of the neurodevelopmental toxicity of perchlorate is mediation through reduction of maternal serum T4 and perturbation of maternal and fetal thyroid homeostasis. OEHHA agrees that there could be direct fetal effects, and that the data are inadequate to define the fetal dose-response for any such effects. This is the justification for use of the most sensitive known effect, plus an uncertainty factor, in the development of the PHG.

Comment 4: *U.S. EPA suggested a more detailed discussion on study design, data quality, and level of resolution for inference possible from the ecological epidemiological studies.*

Response 4: OEHHA has provided a more detailed discussion of the ecological studies.

Comment 5: *U.S. EPA suggested that a reduced form of perchlorate may enter the thyroid and this reinforces the concern that the toxic effects of perchlorate should not be equated with iodide deficiency as a disease state.*

Response 5: It is not clear what is meant by "reduced form of perchlorate." Based on the scientific information available, perchlorate ion is believed to be translocated intact (unchanged) into thyroid cells. While we agree that perchlorate can affect the sodium/iodide symporter (NIS) in several tissues, the identified toxic effects of low-dose perchlorate appear to be related to the disruption of thyroid hormone homeostasis, similar to the effects of an iodide deficiency.

Comment 6: *U.S. EPA suggested that OEHHA add open burn/open detonation operations as sources of contamination to the production and uses section. It is also pointed out that the producer of Chilean caliche has changed its practice to eliminate the potential perchlorate contamination.*

Response 6: The suggested changes have been made to the final PHG document.

Comment 7: *U.S. EPA relayed a concern of the National Exposure Research Laboratory that advocates caution in interpreting the data on uptake of perchlorate into lettuce and exposure estimates.*

Response 7: It should be noted that this comment referred to reliance on the data available in early 2002. Though comprehensive food survey data are not yet available, there now are several reports on concentrations of perchlorate in lettuce, cucumbers, strawberries, grass, cow's milk, and breast milk (Kirk *et al*., 2003; Smith and Jackson, 2003). The relative source contribution parameter used in the calculation of the PHG is 0.6 (60 percent).

Comment 8: *U.S. EPA suggested that the discussion of shower droplet size as another factor that would mitigate the potential for inhalation absorption would help to alleviate public concerns. Likewise, discussion of the importance of mass median aerodynamic diameter (MMAD) to inhalation of occupational dusts would greatly enhance the metabolism and pharmacokinetics section.*

Response 8: The shower droplet size issue has been addressed in the later versions of the document. It seems inappropriate to provide a detailed discussion of MMAD in this section. The draft stated that inhalation of airborne perchlorate particles could be an important exposure route in occupational settings. Lamm *et al*. (1999) studied a group of workers in a perchlorate production plant and reported that there was a correlation between airborne perchlorate dust concentration and the amount of perchlorate excreted in urine. It should be noted that particles that are too large to reach the alveolae can be carried upward by the ciliary escalator in the upper respiratory system and subsequently ingested, which contributes to the overall perchlorate dose.

Comment 9: "The top of page 18 attributes differences in some rat studies to differences in routes of administration but the influence of this modulation when discussing the human occupational data is omitted. Fail *et al.* (1999) have shown strain differences in endocrine modulation that are a more plausible reason for the variability than differences in diet."

Response 9: This paragraph tries to reconcile the differences in biological half-life of perchlorate reported in several studies. The explanations provided are speculative. Animal strain differences probably have a profound influence on endocrine modulation, but it is not clear how this relates to the different biological half-lives reported by various researchers.

Comment 10: "The most notable omission from this section was the entirety of the modeling effort performed at Wright-Patterson AFB, particularly for the different life stages and the human clinical studies. Many insights from these analyses were ignored in the PHG document."

Response 10: Detailed PBPK modeling results and interpretations are reported in the U.S. EPA (2002) perchlorate risk assessment. This effort was not duplicated by OEHHA because OEHHA developed the proposed PHG based primarily on the human data. In the PBPK work published by Clewell *et al*. (2003), they estimated that the serum perchlorate dose of the neonate rat is lower than that of the lactating rat as well as the pregnant rat. In terms of inhibition of thyroid iodide uptake, Clewell *et al*. (2003) predicted that the fetal rat is the most sensitive subgroup at low doses (0.01–0.1 mg/kg-day), compared with the male rat, the pregnant rat and the lactating rat.

One of the major unknowns in this evaluation for which PBPK data would be extremely valuable is extrapolation of the iodine inhibitory effect to potential effects on human fetal neurodevelopment, which is not covered in the present PBPK models.

Comment 11: *The PHG document does not accurately present the analyses of the brain morphometry data and conclusions.*

Response 11: OEHHA did not perform a detailed evaluation of these animal toxicity data. The section on animal toxicity defers in many cases to the results and evaluations provided by U.S. EPA.

Comment 12: "The discussion on pages 4 and 76 is inconsistent with that on page 22 with respect to the lack of reversibility in the effects on T4 and TSH after 30-days recovery in the Springborn (1998) study. This lack of reversibility and the duration-dependent changes in the other sacrifice points of the 90-day studies coupled with the observation of tumors in the F1 generation of the reproductive study collectively support a concern for the potential for resetting the HPT axis with prolonged exposure. This has profound implications for the lack of chronic data on this chemical and should be factored in to UF considerations."

Response 12: We do not agree that the discussions on pages 4 and 22 are inconsistent. In both pages it was stated that increases of absolute and relative thyroid/parathyroid weights observed in rats exposed to the highest dose (10 mg/kg-day) of ammonium perchlorate were reversible (Springborn Laboratories, 1998). However, more details were given on page 22 which added that "full recovery from the effects on serum TSH of all the treated animals was observed at the 120 day evaluation. Only partial recovery was observed for serum T4 in all the dose groups at the 120 day evaluation, however." The lack of total recovery refers to the serum T4 levels, not the increases of absolute and relative thyroid/parathyroid weights. Two of the three reviewers in our second University of California peer review recommended that an uncertainty factor not be applied for the lack of chronic studies and the limitation of the toxicity database (OEHHA, 2004).

Comment 13: "The lack of an explicit link between the iodide deficiency literature and the perchlorate clinical data is exacerbated by the decision to remove the quantitative presentation of the Greer *et al.* (2000, 2002) and Lawrence *et al*. (2000, 2001) data. … We have summarized the NOAEL and LOAEL from the PHG document in Table 1. Data on urinary iodide for the Lawrence *et al.* (2000) study suggest that dietary iodine intake was more than adequate while no information on dietary iodine status was provided in the PHG report for the Greer *et al*. (2000, 2002 - In Press) data."

Response 13: Quantitative data from Greer *et al.* (2002) and Lawrence *et al*. (2000, 2001) studies are provided in the draft and the final PHG document. Dietary iodine information was not provided in the Greer *et al*. (2002) report.

Comment 14: "It is not discernible at all to the naive reader that the Lawrence *et al*. (2001) study is in fact only a letter to the editor as it appears to be given as much weight and discussion as those that have appeared in the peer reviewed literature. It also seems contradictory that the data from both of these studies are given much less scrutiny and reporting than some of the studies from the iodide deficiency literature which are not featured in the quantitative derivation. We again call attention to the serious deficiencies that precluded the use of these data for the PBPK model development noted in the QA/QC report (Merrill, 2001a). Similar reservations in relying on these data to calculate a level protective of public health would seem prudent."

Response 14: We acknowledge the scientific issues raised with regard to using the Lawrence *et al.* (2001) data. In the final PHG document, the BMDL was derived from the Greer *et al*. (2002) thyroidal iodide uptake data set.

Comment 15: "No critical evaluation of the merits of the analysis provided by the authors in the Greer *et al*. (2000, 2002 – In Press) abstract and manuscript is provided. The statisticians on our expert panel questioned the log transform that linearizes the low doses. The power analysis that EPA performed that demonstrated that the limited number of subjects at the low dose is relevant to this designation and was not included. Other reviewers also did not agree that the degree of iodide inhibition seen in this study

should be viewed as a NOAEL. These comments were based on both the duration of the study (discussed below) and the meaning of the magnitude of perturbations observed when viewed from a population perspective. The reviewers emphasized that healthy adult humans store thyroid hormones sufficient to supply several week's requirements even after blockage of the iodide uptake mechanism in the thyroid. In light of those uncertainties, it is difficult to assert that the degree of iodide inhibition is a LOAEL, especially when integrated with the laboratory animal evidence."

Response 15: OEHHA did not rely on the analysis presented in the paper published by Greer *et al*. (2002) in developing a PHG for perchlorate. OEHHA used the thyroidal iodide uptake data provided by Greer *et al*. (2002) and performed our own benchmark dose analysis using the U.S. EPA benchmark dose software. The issues raised in the comment regarding the power analysis and the designation of a NOAEL are addressed by using the benchmark dose approach to develop a point of departure in the risk assessment. The model selected was the Hill model, which is consistent with the known mechanism of perchlorate, competitive inhibition of NIS. In our analysis, OEHHA did not log-transform the data. The way OEHHA analyzed the Greer *et al*. data has been considered acceptable by the reviewers in the second University of California peer review (OEHHA, 2004).

OEHHA agrees with U.S. EPA that the study population does not mirror the general population. For instance, pregnant women, infants, and small children were not included in the study. Furthermore, the study population appeared to have a relatively high iodine intake. For this reason, an uncertainty factor was used in the development of the PHG. However, it is important to note that the critical end-point used by OEHHA is inhibition of thyroidal iodide uptake, not changes in serum T3, T4, or TSH levels.

Comment 16: "These reviewer comments regarding the reserve of the colloid in humans has relevance to the discussion on the bottom of page 80. It seems inconsistent to invoke iodide deficiency as a model for the effects of perchlorate and then argue that humans that are not iodide deficient maintain serum T3 and T4 levels. That is because they have colloidal stores and this is relevant only with respect to critically evaluating the study design of the Greer *et al*. (2002 - in press). Assuming normal colloid stores is not protective of public health. Furthermore, as pointed out in the document, colloid reserve can be depleted from a number of environmental insults in addition to iodide deficiency so that this discussion seems contradictory. The reason for the TSH decrement is an established depletion of TSH prior to its upregulation and the 14-day cut-off is about the correct period for that to occur. We agree with the other factors weakening the argument on the top of page 81."

Response 16: The draft stated "there are short-term exposure data to indicate adult humans that are not iodide deficient are better than rodents in maintaining serum T3, T4 levels when exposed to perchlorate." This claim is supported by human and animal data.

One of OEHHA's goals in selecting the critical endpoint is to prevent the depletion of stored iodide colloid. If perchlorate exposure is kept below the threshold for inhibition of iodide uptake, then there will be no depletion of stored colloid. For the risk assessment,

OEHHA has taken into consideration the possibility of sensitive subpopulations that could have lowered colloid stores in their thyroids.

OEHHA is concerned about the presence of other goitrogens in the environment, and this concern is reflected in the choice of uncertainty factor in the development of the PHG.

Comment 17: "Inhibition of iodine uptake by the thyroid and other tissues appears to be competitive. The lower the iodine concentration relative to the perchlorate concentration (the higher the perchlorate/iodine ratio) the greater the inhibition. Because the nature of the inhibition of uptake is competitive, the effective level would be decreased in iodine deficient individuals as compared to individuals on iodine adequate diets and, thus the intraspecies UF may not be adequate to cover sensitive subpopulations. This also argues to not designate the 0.007 mg/kg-day dose as a NOAEL."

Response 17: The term NOAEL refers to the observation made with the study population, not with the target population. Conventionally an uncertainty factor is applied when there is reason to believe that the target population is different from the study population. It is possible that a lower NOAEL might have been observed if the study population were iodine deficient. However, another commenter argued, using kinetic information and principles, that within the normal range of plasma iodide concentration, plasma iodide should have no impact on the perchlorate NOAEL. We believe that the uncertainty factor applied in the determination of the PHG adequately addresses the uncertainty in this interpretation. Because OEHHA has used a benchmark dose approach to identify the point of departure, the identification of a specific NOAEL is no longer necessary.

Comment 18: "Based on the Total Diet Study Data, for new-born infants there is about a ten-fold difference between the suggested iodine intake and the ten percentile intake. With the pregnant and lactating women there is about a two-fold difference between the estimated average need and the ten percentile intake. Thus, the following additional considerations are warranted with respect to the use of adult human data:

- Calculating an RfD for an infant exposed during the first six months of life using the assumption that the mother was on an iodine deficient diet. Deficits in mental development that occur in infancy can have lifetime consequences.
- Refining the UF for intraspecies and the LOAEL adjustment by including consideration of dietary iodine intake by the susceptible population, pharmacokinetic variability regarding intestinal iodine uptake and transport, and pharmacodynamic differences in the population."

Response 18: When one looks at the tails of the intake distributions in food survey data, it is important to know the time period being analyzed. This is because food intake is highly variable and when the averaging period is short (e.g., three to five days), the spread of the data (including the iodine content) would be more than if the averaging period were to be increased to one month or six months. As the results of the Total Diet Study of 1991-1997 were based upon the USDA food consumption survey data for 1994-

1996 (and laboratory analysis of 306 core foods), the averaging period is likely to be relatively short. Andersen *et al.* (2001) measured monthly urinary iodine excretion of 15 healthy men living in an area of mild to moderate iodine deficiency for a year and found significant intra-individual variability. The coefficient of variation and interquartile range of urinary iodine concentration in individual samples were 57.3 percent and 32.0 µg/L, respectively. However, the coefficient of variation and interquartile range of average annual urinary iodine concentration were only 23.6 percent and 11.7 µg/L, respectively. As we expect there is a correlation between the concentration of iodine in breast milk and the dietary iodine intake of the mother, the contribution of intraindividual variability to the variability of iodine concentration in the breast milk could be significant. The difference between the suggested iodine intake and the tenth percentile intake of newborn infants may not be as high as suggested.

Potential impact of low dietary iodine intake, variation in water intake rate and body weight, and goitrogens in the environment are discussed in the final PHG document. It is not clear how variability of intestinal iodine uptake and transport of iodine would have a significant impact on the threshold of NIS inhibition. As an early effect, reduction of thyroidal iodide uptake is chosen as the critical endpoint. This approach and the identification of the Greer *et al*. (2002) study as the critical study are supported by all the reviewers in the second University of California peer review (OEHHA, 2004).

Comment 19: "The assertion in the PHG document that the differences between the two assessments is due to EPA's reliance on the laboratory animal data was disconcerting. As indicated earlier, the HPT regulatory feedback via the NIS is a highly-conserved and critically important to cellular function across most species and EPA views both the laboratory animal data and human data as mutually informative. The human dose of .007 mg/kg-day is not different from 0.01 mg/kg-day in the laboratory animals. The difference is the view that the level in humans represents a NOAEL as discussed above."

Response 19: OEHHA agrees that the laboratory animal data and human data are mutually informative and supportive. The mode of action of perchlorate is similar in animals and humans. OEHHA chose to develop the PHG based on human data and U.S. EPA selected animal data for the determination of a reference dose for perchlorate. These choices of endpoints also affected the uncertainty factors and the estimated safe doses.

Comment 20: "Because both human clinical studies involved small numbers of euthyroid individuals, none of whom represented the most sensitive population, we agree with the application of the total 10-fold factor for intrahuman variability at a minimum. However, considerable uncertainty remains regarding chronic toxic effects over a lifetime. Even the animal studies that are available have not fully satisfied this issue, resulting in U.S. EPA's use of an uncertainty factor of 3 (half of an order of magnitude) for incomplete information on long-term exposures. We recommend that a factor for duration of effects should be employed if short-term dose human studies continue to form the basis of the State's assessment. If these additional uncertainties were addressed then derivation based on the human data or the laboratory animal data would be identical."

Response 20: Two of the three reviewers in the second University of California peer review (OEHHA, 2004) recommended that an uncertainty factor for the limitations of the database and the limited duration of the human study not be applied, because of the nature of the endpoint. We agree with this logic. Therefore, the suggestion of the commenter is not adopted.

Comment 21: "As before we agree with the use of the adult consumption values to convert the dose-response estimate to a PHG but we are not aware of a citation supporting the use of 65 kg for pregnant women. Comments on caveats with respect to the plant uptake data have bearing on the use of the relative source contribution (RSC) determination."

Response 21: The water consumption rate, body weight, and RSC assumptions have been modified in the final document, reflecting our further study of these issues.

Comments from Dr. Joseph G. Hollowell, Department of Pediatrics, University of Kansas Medical Center

Comment 1: "On page 3, you refer to several papers alleging to speak to iodine deficiency during pregnancy and impaired neuropsychological development. There is no question that thyroxine deficiency during pregnancy can be associated with impaired development. The paper you cite by Man and Jones, 1969 found that low maternal thyroxine levels in plasma as measured using butanolextractable iodine (BEI) was correlated to the impaired development of the offspring studied. Their paper did not conclude nor imply that ID was the cause of the impairments in the children. It is misleading to include that paper to support mild or moderate ID leading to impaired development. Other papers that speak of mild or moderate ID leading to impaired development have to be carefully read to determine what the authors meant by mild to moderate ID and whether that has any relevance to the US population."

Response 1: Points noted. In the final document, the Man and Jones study was used to support a linkage between maternal thyroid deficiency during pregnancy and neuropsychological development of the offspring. The document has been revised to indicate that severe iodine deficiency causes cretinism and less severe iodine deficiency during pregnancy has been linked to adverse neuropsychological development and a reduction of IQ of the child.

Comment 2: *The notion that there are data showing iodine deficiency in the United States was disputed. In a published study, this commenter evaluated iodine excretion levels of the U.S. population and found the population appears to be normal using the WHO criteria for iodine sufficiency. It is pointed out that a finding of 11.7 percent of the population with urinary iodine concentrations <50 µg/L merely represents the fraction of the population with a low iodine intake on the day before the study, not the fraction of the population with iodine deficiency.*

Response 2: We accept this interpretation of the data. The PHG document has been revised to more accurately characterize iodine status in the population.

Comments from Dr. Glen F. Maberly, Rollins School of Public Health, Emory University

Comment 1: "Using these internationally accepted criteria and applying them to the spot urine iodine data of the NHANES I and NHANES studies, we showed (1) that a dramatic reduction of iodine levels in the US population had occurred over the twenty years and (2) that the US population continued still to be NOT iodine deficient. Subsequent to that publication, the analyses of the NHANES III data on thyroid function levels were released and these results reinforced the observation, as there were no perturbations in thyroid function demonstrated in the US population at this time. Further, they pointed out that significantly higher TSH concentrations were found in persons with high iodine output (> 500 µg I / g creatinine) rather in persons with low iodine output."

Response 1: The final document has been revised to indicate that the NHANES III data showed that under the internationally accepted criteria, the general population of the U.S. was not iodine deficient.

Comment 2: *It is pointed out that the prevalence of women with urinary iodine levels below 50 µg/L was greater in NHANES III than in NHANES I, and that* "if the observed trend were to continue over the next decade, then it would be a significant public health concern that women of childbearing age and pregnant women might begin to fall into inadequate iodine nutrition and the deleterious effects might begin to be manifest in the US population." *The author goes on to state that* "overall the trend has reversed itself since the 1990s," *based on a preliminary analysis of the NHANES 2000 data.*

Response 2: Point noted; the discussion has been clarified in the final PHG document.

Comment 3: "A Danish study demonstrated that 7 % of monthly urine iodine measurements indicated severe iodine deficiency among a group of men whose regularly repeated measurements showed that none of them were severely iodine deficient [Andersen *et al*., 2001]. Similarly, Fisher has reported that clinicians allow a minimum 30-day equilibration period to assess the adequacy of a change in iodine dosage because of the day-to-day variation in dietary iodine and rapid excretion [personal communication cited]. Because of the long time it takes for iodine exposure to equilibrate and the great day-to-day variability in iodine exposure for any individual, the single-day single-spot urine data cannot be used to predict what proportion of a population would have a median urine iodine output of <50 µg/L. These data can only be used to describe the central tendency and the dispersion of urinary iodine levels for a particular population. These NHANES surveys are studies for the interpretation of the health of populations, not of individuals." ... *The NHANES data shows there is* "adequate iodine nutrition [in the

population] and NOT that there are certain individuals who are deficient, while others are not."

Response 3: The document has been revised to indicate that the NHANES III data do not provide evidence of iodine deficiency in the U.S. population, and furthermore that the distribution of values is consistent with absence of a deficiency of iodine in the population. However, the data do not preclude the possibility that there are women of childbearing age who receive less than the optimal daily amount of iodide. NAS (2001) suggested a recommended dietary allowance of 220 µg/day for pregnant women.

Comment 4: "From the data that I have reviewed, it would be reasonable to conclude that the current perchlorate levels found in the California drinking water are well below that which would have a deleterious effect on the thyroid function of the population. This conclusion is based on the reported studies that examined the thyroid function in newborns in the US and in Chile and in school children in Chile exposed to maternal and/or individual use of perchlorate-containing water. These data are also reassuring, since they also seem to agree with the observation that the iodine status of the US population in the studies (control and exposed groups) was also iodine replete. The study by Greer et al. (2002) would seem to have demonstrated a threshold exposure for perchlorate inhibition of iodine uptake and to have shown a dose-response curve for perchlorate doses above that threshold exposure. The levels reported in the California drinking water supply fall well below the level that would have an effect on the thyroid, since they would not be expected to materially reduce the amount of iodine available to that gland."

Response 4: In addition to the negative ecological studies cited by the commenter, OEHHA has also identified two positive ecological studies (Brechner *et al.*, 2000; Schwartz, 2001) linking serum hormone changes in newborns to low-level perchlorate exposure. However, there are a number of limitations with the ecological study results, including relatively small sample size, insufficient control of some of the confounding factors, relatively large uncertainty in the exposure estimates, and the fact that the endpoints studied may not be the most sensitive one (i.e., neurological development of fetuses and infants). OEHHA agrees that the mechanistic data available indicate a threshold for perchlorate inhibition of thyroidal iodine uptake. OEHHA used a benchmark dose model to evaluate the Greer *et al.* (2002) data set and define the study threshold. We then attempted to extrapolate to a population threshold, with adequate consideration of uncertainty, by applying a 10-fold uncertainty factor and appropriate exposure factors to develop the public-health protective level for perchlorate in drinking water. We agree that the resulting PHG falls well below the no-effect level defined for healthy adults by the study of Greer *et al.* (2002), but believe the difference is justified for protection of sensitive subpopulations, with an adequate margin of safety, as required by California Health and Safety Code §116365(c).

Comment 5: "In addition to the [human] studies on perchlorate, there are many other studies that demonstrate the general absence of a thyroidal effect from exposures to goitrogens at environmental exposure levels among iodine replete populations. Smoking

is an example of an environmental goitrogenic exposure, probably due to the increase in the serum level of thiocyanate (SCN^-). Thiocyanate (SCN^-) is a major environmental goitrogen, usually through smoking or food. However, it is known that the goitrogenic effects of SCN are mitigated by the iodine nutrition in a population (i.e., the I/SCN ratio) and when a population is iodine replete, there is no perturbation of thyroid function. Thus, similarly, there is no reason to believe that perchlorate would have an adverse effect, particularly where there is no documented iodine deficiency in the population and particularly now that it has been shown to behave like a threshold goitrogen."

Response 5: We are aware of the data showing an association of smoking and goiter in a low iodine intake area. Knudsen *et al*. (2002) performed a cross-sectioned study on patients from two areas in Denmark with urinary iodine levels of 45 µg/L and 61 µg/L. They found thyroid volume was positively associated with smoking habits ($p<0.001$). The association was stronger in the area with the lowest iodine intake. A positive association with smoking was also found for thyroid enlargement and palpable goiter. The fraction of goiter cases attributable to smoking was 49 percent (95 percent confidence interval, 29–65 percent). Another study extends this to observation of effects on iodine status of breast-fed infants of smoking mothers (Laurberg *et al*., 2004). OEHHA agrees with the commenter that iodide status is an important consideration in evaluating the health effects of perchlorate exposure. OEHHA also believes that subpopulations that would be more sensitive to iodine deficiency are likely to exist in the U.S., such as pregnant women and their fetuses, lactating women, infants, and persons with hypoactive thyroids.

Comments from Dr. Delbert A. Fisher, Professor of Pediatrics, Emeritus, UCLA School of Medicine

Comment 1: "Although there is some tendency for thyroid enlargement during pregnancy, there is no evidence that the NOEL for perchlorate would be appreciably different in non-pregnant and pregnant women in early pregnancy. The third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1994 in the United States demonstrates that individuals with low urinary iodine (UI) concentrations (< 50 µg/g creatinine) as compared to those with UI 50-500 µg/g creatinine did not show elevated geometric mean TSH concentration. [11] The NHANES group and others have concluded that spot urine iodine measurements over-predict the prevalence of moderate or severe iodine deficiency."

Response 1: OEHHA agrees that spot urinary iodine over-predicts the spread of the long-term urinary iodine of a population. It follows that spot urinary iodine is not expected to correlate with TSH data.

It is possible that the threshold of NIS inhibition by perchlorate is the same in pregnant and non-pregnant women. However, because pregnancy itself puts stress on the thyroid and because iodine excretion is higher in pregnant women, OEHHA identifies pregnant women with marginal iodine intake as one of the sensitive subpopulations. As discussed in the risk assessment, the potential health consequence of thyroidal NIS inhibition is also greater in pregnant women than in non-pregnant women.

Comment 2: "Liberman *et al*. measured urine and serum iodide in pregnant and postpartum women in the iodine sufficient population of Santiago, Chile, finding mean values during the first, second, and third trimester, and postpartum of 594, 469, 786, and 459 µg/day (urine) and 1.6, 1.8, 1.8, and 1.3 µg/dL (serum), respectively. They concluded that pregnancy in iodine sufficient areas does not have an important influence on circulating concentrations of iodide. A WHO publication regarding the status of iodine in the United States, "Current Iodine Deficiency Disease Status (CIDDS) report of 1995" listed the United States and Canada as "IDD eliminated" based on goiter prevalence."

Response 2: OEHHA agrees that by the internationally accepted criteria, the U.S. is not considered as an area with iodine deficiency. However, as correctly pointed out by the commenter, the PHG has to be protective not only in normal circumstances but also in extraordinary circumstances. One of the goals of the PHG is to protect the embryo/fetus, particularly in a woman with iodine deficiency or marginal iodine deficiency.

Comment 3: "One of the sensitive markers of iodine deficiency in a population is thyroid gland enlargement. Studies of children 6-12 years of age in the United States indicate average sonographic thyroid gland volume less than the WHO normative data. A study of iodine metabolism in neonates in North America (Toronto) quoted by Delange showed a very adequate mean urinary iodine concentration of 148 µg/L and a mean thyroid iodine content of 292 µg."

Response 3: OEHHA agrees that the general population of the U.S. is not iodine deficient. However, this does not eliminate the possibility of a small proportion of individuals with less than optimal dietary iodide intake, and special needs. The PHG is intended to protect such sensitive subgroups within the population, as required by HSC §116365(c).

Comment 4: "[A]vailable information indicates that perchlorate in drinking water has, potentially, adverse effects by way of inhibiting thyroidal iodine uptake causing absolute or relative hypothyroidism. The highest risk populations are pregnant women, neonates, and children. The perchlorate effect is a threshold action at approximately 500 µg/day (or 225 ppb in 2 liters of water). Below this threshold in iodine replete population perchlorate has little or no adverse effects. With iodine sufficiency, this is also true in pregnant women and in children. Available evidence indicates that North America is an iodine-replete region and that levels of iodine in pregnant women and in children are relatively high. The proposed OEHHA PHG value of 6 ppb would seem unnecessarily conservative."

Response 4: Using a benchmark dose approach on the thyroidal iodide uptake data reported by Greer *et al.* (2002), OEHHA determined a BMDL of 0.0037 mg/kg-day. From this effect level observed in a short study in a small population of healthy and iodide-sufficient men and women, an uncertainty factor of 10 is applied to estimate a health-protective level in the entire population, including sensitive subpopulations. By

law, the PHG is required to protect sensitive subpopulations, include multiple exposure routes, and have an adequate margin of safety (HSC §116365 (c)(1)).

Comments from Dr. Mic Stewart, Metropolitan Water District of Southern California

Comment 1: "OEHHA has based the PHG on a precursor event: the inhibition of the thyroid's uptake of iodine. The assumption underlying the use of a precursor in establishing a PHG is that the threshold for adverse effect is the same as the threshold for change in the precursor. As a result, the argument depends critically on a demonstration that there is at least a non-zero probability that the precursor leads to the end point of concern at low-levels of exposure to the contaminant. The draft PHG report does not explicitly demonstrate this linkage."

Response 1: There is expected to be a "margin of safety" between the inhibition of thyroidal iodide uptake and other thyroidal effects such as depression of serum T4, elevation of serum TSH, and enlargement of the thyroid gland. However, the margin is likely to vary from person to person depending on a number of factors, including amount of iodide stored in the thyroid, exposure to other environmental goitrogens, pre-existing thyroid illnesses, and pregnancy. This margin of safety is acknowledged but not numerically incorporated into the calculation of the PHG, since the available data are insufficient to delineate the dose-response. This is one of the reasons that OEHHA applies a relatively small overall uncertainty factor of 10 in the perchlorate risk assessment.

Comment 2: *In the Lawrence et al. and Greer et al. studies cited, perchlorate doses were given to human subjects and followed by an acute dose of iodine to measure the uptake of iodine by the thyroid.* "[T]he acute dose of iodine can saturate the [NIS] sites that are not occupied by perchlorate. This will leave many iodine atoms without a site, resulting in that iodine being excreted before it can be taken up by the thyroid. If iodine instead is taken in slowly (as in daily life), the amount of iodine in the bloodstream competing with perchlorate for absorption sites at any one moment will be much smaller, and the number of sites available for transporting iodine will be larger. The result will be less of an effect on iodine uptake than was the case following a large and acute dose of iodine (as in the experiments). This implies that the NOAEL or LOAEL may be higher under conditions of chronic iodine uptake than indicated by the Lawrence *et al*. and Greer e*t al*. studies."

Response 2: One of the main objectives of the Greer *et al*. (2002) study is to identify the perchlorate dose at which there is little or no thyroidal iodide uptake inhibition, and the number of NIS sites occupied by perchlorate is expected to be relatively small near the NOAEL or LOAEL. For this reason, the impact of the phenomenon suggested by the commenter, if it exists, is not expected to be large.

Comment 3: "The fraction of the population with iodine deficiencies may be overestimated, and so the size of the sensitive sub-populations may be overstated."

Response 3: The PHG document has been revised to acknowledge that the general U.S. population is not expected to be iodine-deficient based on the data provided by the NHANES III survey.

Comment 4: *The relative source contribution of 60 percent used in the calculation of the proposed PHG is based on the results of a study that showed perchlorate bioaccumulated in laboratory-grown lettuce irrigated with water containing 10,000 ppb perchlorate. The relative source contribution assumes the transfer ratio of perchlorate in water to lettuce is the same at low concentrations as it is at high concentrations. Further research is necessary to refine the relative source contribution assumption.*

Response 4: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types.

Comment 5: "The PHG assumes that a pregnant woman weighing 65 kg ingests 2 L of water/day. This assumption significantly overstates daily average ingestion. EPA, based on data collected by the U.S. Department of Agriculture in its 1994-96 Continuing Survey of Food Intakes by Individuals, found that pregnant women ingested, on average, 1.3 L of water per day while lactating women, on average, ingested 1.5 L/day. Although ingestion exceeded 2.3 L/day and 3.0 L/day at the 90^{th} percentile for pregnant and lactating women, respectively, the sample sizes at these percentiles were considered too small to meet minimum reporting requirements."

Response 5: The water consumption rate and body weight of pregnant woman and infant have been revised. They are now obtained from the "Air Toxics Hot Spots Program Risk Assessment Guidelines" (OEHHA, 2000), and are based on water consumption surveys conducted in the U.S.

Comment 6: *Many consumers drink bottled water or have a home treatment device that would lower perchlorate exposure, even if the tap water is contaminated with perchlorate. In Southern California, 38 percent of consumers report they drink bottled water only and 34 percent report that they have home filtration devices.*

Response 6: Although many homes have installed water treatment devices and many individuals drink bottled water on a regular basis, the development of a perchlorate PHG cannot be based on these situations. The PHGs provide estimates of the level that is not anticipated to cause or contribute to adverse health effects, or any significant health risk, for chemicals in drinking water. The establishment of Maximum Contaminant Levels (MCLs) for the chemicals in drinking water, followed by consumer decisions about their uses of the water, represent the subsequent steps involving risk management decisions about the chemicals.

Comments from Richard B. Rothman, MD, PhD, Fairfax, VA

Comment 1: *The commenter provided pharmacokinetic arguments to show that within the normal range of plasma iodide, inhibition of thyroidal iodide uptake by perchlorate would not be altered by lowering plasma iodide, so that the NOEL for perchlorate as identified in the Greer et al. study should be unaffected by the iodine status of the participants.*

Response 1: OEHHA agrees that if the assumptions and parameter values used in the argument are correct, the effect of plasma iodide on the NIS inhibition threshold should be quite small. However, other commenters have provided different interpretations of the available data. OEHHA considers this to be one of the uncertainties in the risk assessment.

Comments from Dr. Val Abbassi, Division of Pediatric Endocrinology, Georgetown University School of Medicine

Comment 1: *Occupational studies have demonstrated that perchlorate exposures at 34 mg/workday and below do not adversely affect the T4 or TSH levels. Data from Greer et al. (2002) demonstrated a threshold for iodine uptake inhibition of approximately 0.5 mg/day or an equivalency to a water level of 250 ppb perchlorate.*

Response 1: There are a number of concerns if changes in serum T4 or TSH level were selected as the critical endpoint instead of the inhibition of thyroidal iodide uptake. The thresholds of serum T4 or TSH change are likely to be affected by dietary iodide intake, exposure duration to perchlorate, and the amount of iodide stored in the thyroid. The more-complicated dose response relationships between perchlorate exposure and serum T4 or TSH changes in animals and humans means that uncertainty in the determination of the thresholds would be greater than for inhibition of iodide uptake. A monotonic dose-response relationship has been observed between iodide uptake inhibition and perchlorate

dose (Greer *et al*., 2002), which helps minimize the uncertainty in the use of this endpoint to estimate a negligible risk level.

Lamm *et al.* (1999) studied thyroid function of three groups of workers exposed to different levels of perchlorate via inhalation. No differences in thyroid-function parameters were reported between the exposed workers and the controls. However, it is important to realize that the perchlorate workers were on 12-hour shifts and they worked for three consecutive days and then were off for three consecutive days, while the serum half-life of perchlorate is about 8 hours. Lamm *et al.* reported that perchlorate level in the system dropped to a very low level on the second and the third "off" day. It can be argued that the thyroid of the exposed worker would have a chance to replenish its iodide storage during that time. OEHHA does not believe the results of this study can be used to assess the health effects of perchlorate in drinking water.

Comment 2: *The demonstration of a threshold for inhibition of iodine uptake by perchlorate is important because it demonstrates that if exposure is brought below the threshold it will be safe. Perchlorate exposure below the threshold will not aggravate the problem of a person with hypothyroidism. Similarly, perchlorate exposure below the threshold will not aggravate the iodine deficiency problem (e.g., maternal goiter).*

Response 2: OEHHA agrees; this idea forms the basis of the determination of the PHG. The critical task is to accurately estimate the threshold, with adequate provision for uncertainty in the estimate in order to protect sensitive populations.

Comment 3: "It is reasonable to assume for any particular individual, that the pharmacokinetics of all of their NIS sites is similar, independent of the tissue the NIS is found in. Thus, the threshold level for NIS in the breast or in the placenta should be the same as the threshold for the NIS in the thyroid. Differences may occur from tissue to tissue as to how many active NIS sites are present, but their pharmacokinetics should remain the same."

Response 3: This may be a valid assumption, although data are inadequate to document the effect of a given level of interaction with NIS in different tissues, such as inhibition by perchlorate of iodine secretion into human breast milk. Also, it is known that the regulation of NIS in different tissues is mediated by different hormones. For instance, NIS in thyroid tissue is regulated by TSH, while NIS in mammary gland tissue is regulated by prolactin (Rillema and Rowady, 1997). Thus the pharmacodynamics may differ among tissues.

Comments from Steven H. Lamm, Arnold Engel and Offie Porat Soldin, Consultants in Epidemiology and Occupational Health, Inc.

Comment 1: *The commenters provided their interpretation of (a) medical experience with perchlorate, (b) occupational health studies, and (c) environmental health studies.*

Response 1: OEHHA appreciates the insights provided by this discussion. Many of the strengths and weaknesses of these three types of studies have been discussed in the PHG document.

Comment 2: *The commenters provided their interpretation of the two Lawrence et al. studies (2000, 2001) and the Greer et al. (2002) study. It was suggested that based on the reported data by Greer et al., the no effect level of the inhibition of thyroidal iodide uptake ranged from 5.2 µg/kg-day to 6.4 µg/kg-day. It was also suggested that the highest dose in the Greer et al. study, 35 mg/day or 0.5 mg/kg-day, could be identified as a NOAEL for perchlorate in humans, and a safe exposure level.*

Response 2: As described in detail in the PHG document, OEHHA applied the benchmark dose approach in analyzing the Greer *et al*. thyroidal iodide uptake data and identified a point of departure of 0.0037 mg/kg-day (3.7 µg/kg-day). This analysis takes into consideration the variability exhibited in the data set.

OEHHA does not agree that serum T4 or serum TSH data reported by Greer *et al*. (2002) are suitable for the determination of a health protective drinking water level for perchlorate. Impairment of thyroid function and changes in serum T4 and TSH levels are dependent on perchlorate dose and exposure duration as well as dietary iodide intake and the amount of iodide stored in the thyroid. The volunteers in the Greer *et al*. study had relatively high iodide intake levels and short exposure duration (14 days). At the highest dose, 35 mg/day, Greer *et al*. observed 65-70 percent thyroidal iodide uptake inhibition among the exposed subjects. If the exposure duration were extended, it is likely that the iodide stored in the thyroid would be reduced and thyroid function would be impaired. OEHHA disagrees with the statement "the congruence of results from these three very different types of study yield for me the conclusion that a human dose rate of perchlorate of 35 - 50 milligrams per day is a safe exposure for most people in the United States."

Comment 3: *The commenters alerted OEHHA to an unpublished study on the lack of correlation between neurobehavioral conditions of childhood including attention deficit hyperactivity disorder (ADHD) and low neonatal thyroxine levels.*

Response 3: It is difficult for OEHHA to critically review an unpublished study. However, the lack of correlation does not exclude the possibility that low maternal serum T4 or low fetal serum T4 during the first and second trimester are related to abnormal brain development.

Comment 4: "The sensitive populations that OEHHA identifies are the populations at risk of hypothyroidism, not the populations at risk from some iodine uptake inhibition."

Response 4: OEHHA identified pregnant women as the sensitive population because of the increased need of iodine and iodine excretion during pregnancy. This increases the likelihood of less than optimal iodide uptake into the thyroid. Fetuses are at risk because reduction in iodide transfer in the placenta and impairment of maternal thyroid function can lead to abnormal brain development. In addition, the amount of iodide stored in the

thyroid of fetuses and neonates is small relative to the need, thus the inherent safety margin between iodide uptake inhibition and disruption of thyroid hormone balance is smaller in fetuses and neonates than that in iodine-sufficient adults. The goal of the PHG is to avoid the inhibition of NIS and prevent the associated undesirable health effects.

Comment 5: "The only population in the United States that might be iodine-insufficient is potentially the vegan community. ... If there is a problem for California Vegans, that should first be determined and then be addressed through public health education of the community. That has nothing to do with perchlorate."

Response 5: In the PHG document, OEHHA has discussed the increased risk of iodine deficiency of individuals on a vegetarian diet, and the potential for other iodine-deficient subpopulations. The law mandates that the PHG be health-protective for all segments of the population, including sensitive subgroups (HSC §116365 (c)(1)). OEHHA agrees with the commenters that based on the NHANES III data, there is no evidence that there is iodine deficiency in the U.S, on a population basis. However, the data cannot provide an answer to the question of whether there are iodine deficient individuals in the U.S.

Comments from Arnold Engel and Steven H. Lamm, Consultants in Epidemiology and Occupational Health, Inc.

Comment 1: *The commenters analyzed the NHANES III data and suggested that there was no association between low urine iodine levels and hypothyroidism as measured by low serum T4 or high serum TSH.*

Response 1: The lack of correlation between urine iodine and serum T4 or TSH is not surprising because of the high variability of spot urinary iodine. The commenters are aware of this limitation and acknowledged that a single spot urine may not accurately reflect the overall iodine status of an individual over a long period of time.

OEHHA agrees with the commenters that based on the NHANES III data, there is no evidence that there is iodine deficiency in the U.S, on a population basis. However, the data cannot provide an answer to the question of whether there are iodine deficient individuals in the U.S.

Comment 2: *The commenters analyzed the NHANES III data and suggested that the observed low urine iodine levels (<50 µg/L) are mainly attributable to low urine creatinine level. It was suggested that urinary dilution alone accounts for about 80 percent of the low urine iodine levels observed in the study population.*

Response 2: Based on the graphs presented by the commenter there seems to be a correlation between low iodine output (<50 µg/L) and low creatinine concentration in urine. It is not clear if similar results would be obtained if the cutoff point were at some other value (e.g., <100 µg/L). It is also not clear if different ethnic groups would have different urine creatinine concentrations. Without further analysis, it is premature to

conclude that the low urinary iodine data can be mostly explained by urinary dilution.

Comment 3: *The commenters suggested that daily variation in iodine nutrition including days with less than ideal iodine intake amounts (<50 µg/L output) does not affect thyroid hormone levels.*

Response 3: OEHHA agrees that for adults with adequate thyroid iodide storage, this is probably the case. However, it is important to note that if there is a sustained decrease in iodine intake, then eventually, the imbalance in supply and demand would reduce the amount of iodide stored in the thyroid and impair the normal production and secretion of thyroid hormones. The situation is different in fetuses and neonates, for the amount of iodide stored in their thyroid is estimated to last only days, not weeks or months, as is the case in iodide-sufficient adults (van den Hove *et al*., 1999).

Comments from Gretchen M. Bruce and Richard C. Pleus, Intertox, Inc.

Comment 1: "In its draft risk assessment for perchlorate, ...OEHHA proposes to base its PHG for perchlorate on a "level that does not inhibit iodide absorption by the thyroid nor cause release of iodide from the thyroid." OEHHA asserts that "[e]ven moderate to mild iodine deficiency or hypothyroidism during pregnancy has been linked to adverse neuropsychological development and a reduction of IQ of the child" and identifies several scholarly studies that it suggests provide a scientific basis for these inferences." *However, the commenters disagree that the studies cited by OEHHA provide scientific support for OEHHA's inferences.* "[S]tudies cited pertain to populations that were severely iodide deficient and thus very unlike the iodine-replete population of California. Still other studies concern children who were diagnosed with severe hypothyroidism despite residing in an iodine-replete region. These studies provide no evidence that iodine deficiency had anything to do with these children's condition, and substantial evidence that it did not. None of the studies cited by OEHHA actually identified effects in populations that were *mildly to moderately* iodine deficient or hypothyroid. Each population studied consisted of subjects who were *severely* iodine deficient, *severely* hypothyroid, or had thyroid hormone or thyroid stimulating hormone (TSH) levels well outside the normal range associated with euthyroid individuals. Several studies consisted of subjects living under conditions of *severe* economic distress."

Response 1: OEHHA has revised the statement "even moderate to mild iodine deficiency or hypothyroidism during pregnancy has been linked to adverse neuropsychological development and a reduction of IQ of the child" to "even less than severe iodine deficiency or hypothyroidism during pregnancy has been linked to adverse neuropsychological development and a reduction of IQ of the child."

As cited in the revised risk assessment, Pop *et al.* (1999), Haddow *et al.* (1999), and Klein *et al.* (2001) studied pregnant women in areas with sufficient iodide intake (e.g., in Veldhoven, Netherlands, and in Maine). It was found that women with low free T4 or high TSH were more likely to give birth to offspring with low IQ scores. The fact that some of the women can be classified as hypothyroid does not make these study results

irrelevant. First, we do not know the causes of the hypothyroidism, and second, perchlorate exposure may worsen the hypothyroidism.

Furthermore, pregnant women are identified as a sensitive subgroup because pregnancy itself constitutes a stress on the thyroid. Thyroid enlargement was found to be associated with pregnancy in women with marginal iodine deficiency (Glinoer *et al.*, 1992; Smyth *et al.*, 1997; Kung *et al.*, 2000). Several clinical reports indicate that during pregnancy it is necessary to increase T4 doses of women previously diagnosed with hypothyroidism (Kaplan, 1992; Girling and de Swiet, 1992; Tamaki *et al.*, 1990). Perchlorate exposure of pregnant women with marginal iodine deficiency may increase the risk of thyroid disorder.

Comment 2: "It appears that OEHHA also has a weak statutory basis for its inferences and conclusions. OEHHA's inferences are not derived from "the *most current principles, practices, and methods* used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment, and toxicology" [emphasis added], as required by law. Further, OEHHA appears to have identified as a subgroup of special concern women who are iodine deficient. While the law expressly directs OEHHA to take account of subgroups that "comprise a meaningful portion of the population," there is no evidence that iodine deficiency exists at all in California and substantial evidence that it does not. By law, OEHHA also is required to set public health goals equal to adverse effect thresholds where such thresholds exist. There is credible and reliable scientific information concerning the level of perchlorate exposure below which iodine uptake is not inhibited, but OEHHA has not fully utilized this information. This is particularly problematic insofar as the identified threshold is for a non-adverse effect (*i.e.*, iodine uptake inhibition) that is substantially below the exposure level necessary to cause *bona fide* adverse effects (*e.g.*, clinical or subclinical hypothyroidism) associated with perchlorate exposure in humans."

Response 2: OEHHA has followed the risk assessment principles and guidelines of both Cal/EPA and U.S. EPA in developing the perchlorate PHG. Health and Safety Code, Section 116365 requires OEHHA to develop PHGs in accordance with several criteria, including the following:

- PHGs for acutely toxic substances shall be set at levels which avoid any known or anticipated adverse effects on public health, with an adequate margin of safety.
- Adverse health effects must be considered for "subgroups that comprise a meaningful portion of the general population, including but not limited to, infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subgroups that are identifiable as being at greater risk of adverse health effects than the general population."
- Consideration of "the relationship between exposure to the contaminant and increased body burden, and the degree to which increased body burden levels alter physiological function or structure in a manner that may significantly increase the risk of illness."

- Synergistic effects resulting from exposure to or interaction between two or more contaminants, and additive effects from exposure to the contaminant from other routes or sources.

The PHG on perchlorate was developed by experienced risk assessors, is based on good science, and is consistent with the criteria shown above. Studies on incidence of hypothyroidism in iodine-sufficient populations indicate the presence of subgroups with various causes of thyroid disease that might be affected by perchlorate (Lind, 1998; Milakovic, 2001), and the distribution of iodine excretion values in the U.S. is not inconsistent with a small population of low-iodide-intake individuals. In addition, it has been reported that subpopulations with restrictive dietary practices may be at risk for insufficient iodine consumption (Lightowler and Davies, 1998; Appleby *et al.*, 1999). Ensuring protection of potentially at-risk populations by including an uncertainty factor consistent with professional judgment regarding estimated variability among humans is standard risk assessment practice. Comments from the University of California scientific peer reviewers were generally favorable regarding the approach, methods, and techniques used in the perchlorate risk assessment (OEHHA, 2004).

Comment 3: "Other components of the "link" asserted by OEHHA are also incomplete, since all of the studies OEHHA cites possess etiological factors or confounding variables that make their findings irrelevant to the population of California and the mode of action for perchlorate. All of the studies are based on populations that are severely iodine deficient or the iodine status of the population is not discussed but the population resides in an area known to be iodine-replete. Observations from studies of *severe* iodine deficiency cannot be used to draw inferences about effects in regions of *mild* iodine deficiency and, in regions that are iodine-replete, any reported hypothyroidism likely results from etiologies unassociated with iodine deficiency."

Response 3: OEHHA agrees that many subjects of the studies cited in the PHG document suffered from iodine deficiency. However, it is not definitive whether there are no individuals suffering from iodine deficiency or marginal iodine deficiency in California, especially among the sensitive subgroups such as pregnant women, infants, and small children, and among populations with restrictive diets.

Some studies cited in the PHG document were performed in subjects with mild or marginal iodine deficiency. For example, Smyth *et al.* (1997) found an association between pregnancy and thyroid volume and the median urinary iodine of the subjects was 82 µg/day. Similar findings were reported by Kung *et al*. (2000); the median urine iodine concentration measured in the study was 98 µg/L, which was close to the World Health Organization cut-off value of 100 µg/L for iodine sufficiency. Observed effects of iodine deficiency in any human population are clearly relevant to interpretation of effects of iodine deficiency.

Comment 4: "Although OEHHA asserts that approximately 15 percent of U.S. women of childbearing age may be iodine deficient (based on NHANES III data from 1988-1994 showing that 14.9% of women had urinary iodine levels below 50 µg/L as determined

from single "spot" samples), this assertion appears to be the result of a simple misinterpretation of the NHANES data. ... Population variability would likely have declined dramatically if multiple measurements had been taken, and given the absence of iodine deficiency disorder in the United States, it is quite likely that few if any of these women were truly iodine deficient. Further, no association between low urinary iodine levels and high thyroid stimulating hormone (TSH) or low thyroid hormone (T_4) levels has been shown, indicating that iodine deficiency is not associated with hypothyroidism."

Response 4: The final document has been revised to show that the general population of the U.S. is considered to be iodine-sufficient, according to the NHANES III survey data. However, the NHANES III data show a drastic drop in urinary iodine levels compared to those reported in NHANES I, demonstrating a trend towards reduced iodine intake. The NHANES III data indicate there is a possibility that some pregnant and lactating women are getting less than the optimal amount of iodine from their diet.

Comment 5: Our review of the OEHHA risk assessment, however, reveals that OEHHA presents no scientific evidence that low-level perchlorate exposure may "cause chronic disease." OEHHA's inferences in this regard appear to revolve around its unsupported assertions of the possibility of neuropsychological effects associated with mild iodine deficiency or maternal hypothyroidism.

Response 5: Iodine is an essential nutrient, and perchlorate exposure interferes with its uptake into the thyroid, which could result in developmental disorders. The consequence of a reduced thyroidal uptake of iodine is likely to vary in a population depending on the dietary iodide intake, duration of exposure, amount of iodide stored in the thyroid, pregnancy, or other pre-existing thyroid illnesses. With a goal of protecting the sensitive subgroups in the population, OEHHA identified the inhibition of NIS by perchlorate as the critical endpoint. Clearly, preventing inhibition of iodine uptake into the thyroid by perchlorate will prevent adverse effects such as thyroid enlargement in pregnant women or other sensitive endpoints. OEHHA does not agree that tolerating a "mild iodine deficiency or maternal hypothyroidism" associated with low-level exposure to perchlorate would be protective of public health.

Comment 6: "OEHHA's inferences do not comport with the requirement in California Health and Safety Code § 116365 (c)(1)(D) which says "[i]f adequate scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the public health goal should be set at that threshold." Greer *et al*. (2002) demonstrates the existence of a threshold for inhibition of iodine uptake by perchlorate at a drinking water equivalent concentration of 200 ppb. Moreover, this is clearly a "safe" threshold since it is *not* a threshold for adverse effects. Rather, it is a threshold for a biochemical phenomenon that is both a sensitive and distant precursor for adverse effects and a normal phenomenon whose occurrence is best characterized as mundane."

Response 6: The Greer *et al*. (2002) data were used by OEHHA in developing a PHG for perchlorate. An overall uncertainty factor of 10 was applied in the assessment to account for the differences between the study population and the sensitive populations identified.

This is consistent with the mandate in HSC §116365(c)(1)(A), which says that "The public health goal shall be set at the level at which no known or anticipated adverse effects on health occur, with an adequate margin of safety." The mean dose-response threshold in healthy non-pregnant, euthyroid adults, as in the Greer *et al.* study, cannot logically be inferred to be the "safe dose response threshold" for all members of a population, including sensitive subgroups (see HSC §116365(c)(1)(C)(iii)).

Comment 7: "In all studies cited by OEHHA, populations with demonstrated neurobehavioral deficits are associated with *severe* iodine deficiency or significant hypothyroidism. None of the studies cited by OEHHA provide evidence of adverse effects in populations that were *mildly to moderately* iodine deficient or *mildly* hypothyroid. Evidence of severity in these studies is demonstrated by high rates of goiter or endemic cretinism, significantly reduced neonate skeletal maturity, or significantly affected neonatal or maternal hormone levels [*e.g.*, increased thyroid stimulating hormone (TSH) or decreased thyroxine (T_4)]. Neurobehavioral effects in these populations are not surprising, since a well-established association has been demonstrated between severe iodine deficiency or severe hypothyroidism and adverse neurobehavioral effects in children, such as lowering of IQ. However, it is scientifically inappropriate for OEHHA to draw inferences about the potential for adverse effects among *mildly* affected populations from studies in which baseline conditions are *severe*."

Response 7: OEHHA agrees that some of the studies cited in the document were conducted in areas with moderate iodine deficiency, and that the severity of neurobehavioral deficits in offspring should be proportional to the severity of maternal iodine deficiency. Studies in populations with various degrees of deficiency are appropriate to define the dose-response relationships. Offspring of mothers with marginal iodine deficiency are only one of the sensitive populations identified; another sensitive subgroup is the pregnant women. For instance, Smyth *et al.* (1997) found an association between pregnancy and thyroid volume while the median urinary iodine of the subjects was 82 µg/day. Similar findings have been reported by Kung *et al.* (2000), in which the median urine iodine concentration was 98 µg/L. Values for these populations are close to the World Health Organization cut-off value of 100 µg/L for iodine sufficiency. The median urinary iodine in women of child-bearing age derived from the NHANES III study was 128 µg/L (Hollowell *et al*., 1998), only 30 percent higher than the subjects in the Kung *et al*. study.

Comments from John P. Gibbs, Kerr-McGee Corporation

Comment 1: *Occupational studies (Gibbs et al., 1998; Lamm et al., 1999) demonstrated no hormonal effects attributable to chronic perchlorate exposure at levels similar to doses used in 14-day volunteer studies by Greer et al. (2002). Risk assessment procedures do not warrant application of an uncertainty factor of 3 for extrapolating from short term to chronic exposure in this case. An assumed NOAEL as the starting point for use of an uncertainty factor should be based on evidence of a clinically significant harmful effect, not a threshold for a precursor effect.*

Response 1: Gibbs *et al*. (1998) measured 15 male and 3 female workers' exposure to perchlorate dust over a single workshift and compared their thyroid function parameters to a group of workers not exposed to perchlorate. They found the exposure was not associated with any impairment of thyroid function. The interpretation of the study result is difficult because of: (a) small sample size, (b) uncertain total exposure duration (not discussed in the paper), (c) uncertainty associated with the amount of exposure (some workers wore respirators during the shift; when this occurred, the assumed exposure concentration was decreased by 65 percent, but no justification for this adjustment was given), and (d) the study period might not be sufficiently long, as there is a lag time between perchlorate exposure and changes in thyroid function parameters.

Lamm *et al.* (1999) reported a cross-sectional study on 37 workers exposed to perchlorate, compared to 21 workers not exposed to perchlorate. Both inhalation perchlorate dose and urinary perchlorate excretion were estimated for each exposed worker. No correlation was found between perchlorate exposure and thyroid function test results. The study result is limited by (a) lack of exposure history prior to the study, (b) iodide status of the workers is not known, and (c) perchlorate exposure was intermittent (the work schedule was on three days, off three days). As the biological half-life of perchlorate in human is only 8 hours, the intermittent nature of the exposure might have lessened the impact of perchlorate exposure on the thyroid.

Because of the limitations of the above studies, it is difficult to use them to establish a NOAEL for effect of perchlorate on thyroid function. OEHHA agrees with the commenter that there is likely a margin of safety between the precursor effect (NIS inhibition) and other adverse health effects (such as decrease of serum T3 and T4) for most people. However, this margin depends on a number of factors (dietary iodide intake, amount of iodide stored in the thyroid, and exposure duration), and is likely to vary among individuals in a population. In order to be protective of sensitive subgroups that may be marginally iodine deficient, OEHHA identifies the reduction in thyroidal iodide uptake as the critical endpoint for the development of the PHG.

In the final risk assessment, the 3-fold uncertainty factor was not applied for extrapolating from short term to chronic exposure and for database limitation.

Comment 2: "OEHHA need not be concerned that the Lamm study is not reflective of true chronic exposure. The workers in the Lamm study cycled 3-12 hour shifts followed by three days off. In a figure from the Lamm study, it is apparent that worker's urine perchlorate levels approached 100 ppm after three consecutive 12-hour shifts after which they declined but were still at or above 100 ppb after three days off. At the end of their three days off, the high exposed group of workers, had urine perchlorate levels comparable to those of Chilean school children chronically exposed – and without intermission – to drinking water with 110 ppb perchlorate. These results show that the supposed "intermittent" nature of worker exposure due to transient periods of nonexposure is of no clinical or interpretive significance and does not contribute to any uncertainty."

Response 2: From the two worker's data indicated in the urinary excretion figure in Lamm *et al.* (1999), it is apparent that urinary perchlorate level varied over three orders

of magnitude (between 0.1 mg/L and 100 mg/L) over six days (three days exposed and three days not exposed), which should certainly be associated with variations in blood perchlorate level and degree of inhibition of thyroid uptake of iodine. At least in theory, iodine uptake during the time when levels of perchlorate in blood were low could replenish the iodide stored in the thyroid and reduce goitrogenic effects of perchlorate. Urinary perchlorate levels were not reported in the paper published by Crump *et al*. (2000). It is also not clear how the Chilean study results can alleviate the concerns about limitations in the data reported by Lamm *et al*. (1999).

Comment 3: "Studies among neonates and school children (Crump *et al.*, 2000) with life-long perchlorate ingestion at levels only slightly below the threshold for iodine uptake inhibition demonstrate no adverse hormonal effects. Recently obtained serum and urine perchlorate levels from the school children study are consistent with those from Greer *et al.* (2002), confirming that exposure/dose characterizations in Crump *et al.* are accurate. In fact, perchlorate dose estimates in this study are comparable in quality to clinical trials and represent life-long exposure in sensitive subpopulations. Any supportable PHG would be at least an order of magnitude higher than the levels OEHHA currently proposes."

Response 3: Crump *et al.* (2000) evaluated TSH levels for all neonates born between February 1996 and January 1999 whose city of origin was Antofagasta, Chanaral, or Taltal (n=11,967), although all data obtained during a 7-month period were excluded from the study because of a laboratory error, leaving 9,784 neonatal records for analysis. The study reported that perchlorate exposure did not raise neonatal TSH levels in Chanaral and Taltal, compared to those in Antofagasta (control). Maternal and neonatal serum T4 levels, indicators of the potential for neurodevelopment of the neonates, were not reported.

Crump *et al.* (2000) also evaluated thyroid functions of school-age children of the three cities. It was found that at an average perchlorate level of 112 µg/L, there was no association between perchlorate in drinking water and mean levels of TSH, T4, free T4, and T3. Interpretation of the study result is made difficult by (a) the small number of water samples taken (25 samples in each city), and (b) high goiter prevalence in all three cities (20 to 26 percent). It is also important to note that blood levels of thyroid and pituitary hormones in school-age children may not be the most sensitive indicator for the health impacts of perchlorate exposure. There are reports showing that reduction of maternal serum T4 during early pregnancy may be linked to IQ reduction in the offspring. Neither maternal serum T4 during pregnancy nor IQ in the offspring was measured in this study.

The mean urinary iodine levels of the schoolchildren in the three cities ranged from 610 µg/L to 770 µg/L; by comparison, the mean and median urinary iodine level of children between 6 and 11 years old derived from the NHANES III data are only 305 µg/L and 237 µg/L, respectively. The relatively high urinary iodine levels and high goiter prevalence of the schoolchildren complicates the interpretation of the Crump *et al*. study.

Developing fetuses and small children are two of the four sensitive subgroups identified in the risk assessment. Pregnant women with marginal iodide intake and individuals with

thyroid disorders are the other two. The goal of the PHG is to protect the general population, including these sensitive subgroups.

Comment 4: "To address the concerns regarding pregnant women and the first trimester fetus as being very sensitive subpopulations, we have commissioned a study of pregnant women in northern Chile. The study is currently underway and the protocol is provided. We urge you to await the results of that study before setting a PHG level for perchlorate."

Response 4: OEHHA has legal mandates and statutory deadlines and cannot postpone the release of a PHG because of the pending release of a new study. However, OEHHA is required to reevaluate and update the risk assessments for PHGs at least every five years or as new toxicological data become available.

Comment 5: "KMOC also requests that any reference to EPA's summary risk characterization of perchlorate expressed as a drinking water equivalent level be deleted from the draft PHG. EPA has not developed or concluded a formal risk assessment in a rulemaking process relevant to the federal or state Safe Drinking Water Act that would substitute for OEHHA's own assessment of the underlying data and studies."

Response 5: The PHG document has been revised and the drinking water equivalent level of perchlorate was removed.

Comments from Renee Sharp, Environmental Working Group.

Comment 1: *Using an adult bodyweight and drinking water concentration is justifiable if...* "The infant is less susceptible to the effects of thyroid hormone disruption than the fetus: if the infant was just as susceptible to the effects it seems that OEHHA would have to use an infant body weight."

Response 1: The milk consumption rate and body weight of an infant is used in one of the exposure scenarios in the revised risk assessment. In a PBPK modeling study reported by Clewell *et al*. (2003), they predicted that while the perchlorate dose on a body weight basis to a nursing rat pup is 6-7 times that of the maternal dose, the internal dose in terms of serum perchlorate concentration of the neonate is actually lower than that of the lactating rat, the pregnant rat, and the male rat, presumably because of rapid perchlorate excretion in the neonate. At low perchlorate doses, they also predicted that the percentage inhibition of thyroidal iodide uptake is highest in the fetal rat, compared to those in the neonate rat, the lactating rat, and the pregnant rat. Although such detailed PBPK models are not yet available for humans, the kinetics and principles revealed in the available studies help inform our risk assessment.

Comment 2: *Using an adult bodyweight and drinking water concentration is justifiable if...* "The infant and the adult have similar needs for iodide relative to bodyweight: if the infant has much higher relative needs than the adult, then the effects of perchlorate are

likely much greater. In a 1996 monograph published by Fisher and Delange that compares iodide requirements in infants and adults, it is estimated that the iodide requirement for premature infants are 15 times higher and requirements for infants aged 0-6 months are 7.5 times higher, compared to adults."

Response 2: To the best of our knowledge, there is no information showing NIS in the thyroid of infants is different from that in the thyroid of adults. If the characteristics of NIS stay the same at different age groups, the blood concentration threshold for the inhibition of NIS would also be the same. The threshold in terms of dose per unit body weight depends on pharmacokinetics of perchlorate in the infant compared to adults. There is some information from pharmacokinetics that blood concentration of perchlorate, at a particular dose, should be less in an infant than in an adult because of a greater volume of distribution and faster elimination in infants (see the previous response). The difference in the need of iodide and the amount of iodide stored in the thyroid affect the immediacy and the severity of thyroid function disruption once there is a reduction in thyroidal iodide uptake.

Comment 3: *Given the concerns described above and the fact that perchlorate may also be concentrated in breast milk, does OEHHA still think a safety factor of only 30 would really provide much margin of safety for infants and children, especially if an adult body weight was continued to be used in deriving a PHG?*

Response 3: The revised PHG document explicitly considers liquid consumption rate and body weight of infants. The estimated exposure is about six-fold higher than the usual adult values. This dose adjustment replaces part of the usual 10-fold uncertainty factor for human variability, thus leading to a lower total uncertainty factor in the calculation. Conceptually, it is plausible that perchlorate can be concentrated in breast milk. At the moment, OEHHA is aware of a single detection of perchlorate in human breast milk. Kirk *et al*. (2003) tested a breast milk sample and found 3-4.5 µg/L of perchlorate using two analytical methods. They also reported that levels of perchlorate in local tap water ranged from below 0.5 µg/L to above 4 µg/L, with a mean value of 2.5 µg/L in the samples in which it exists above the detection limit.

In judging adequacy of the uncertainty factor, one should consider the nature of the endpoint (iodine uptake inhibition), compared to uncertainty factors based on significant adverse effects (developmental defects, death, etc.).

Comment 4: "[A]re you aware that the EPA did not in fact use the Lawrence 2000/2001 studies for their PBPK modeling? Apparently, among other concerns of QA/QC, it appeared that at least some (of the only EIGHT subjects) had not actually taken the entire perchlorate dose. They concluded that "it would be difficult to designate this effect as a [NOAEL] with any confidence. ... Did OEHHA have different feelings about these issues?"

Response 4: We were aware that the U.S. EPA considered the Lawrence *et al.* studies (2000, 2001) inadequate for PBPK modeling. No problems documented in the published information available to us would cause OEHHA to exclude the Lawrence *et al*. studies

from toxicological evaluation. However, the limitations of the data led us to choose the Greer *et al*. (2002) studies for the development of the final PHG. The limitations include: (a) a single dose (10 mg and 3 mg) was used in both studies, (b) a small number of subjects in both studies, and (c) detailed toxicological information was not reported in the Lawrence *et al*. (2001) study.

Comments from the Perchlorate Study Group, an industry association

Comment 1: *On the interpretation of thyroidal iodide uptake inhibition as an adverse effect:* "Inhibition of thyroidal iodine uptake is the recognized site of action of perchlorate and the precursor to any adverse effects. However, the perchlorate dose that causes thyroid hormone changes, the precursor to adverse effects, is much higher than the dose that causes minimal inhibition of iodide uptake. There is a considerable safety margin implicit in basing the PHG on the NOEL for iodide uptake inhibition in iodine sufficient populations, on the order of 50-100 fold."

Response 1: OEHHA agrees with the commenter that there is a margin of safety between the precursor effect (inhibition of iodide uptake) and the other adverse health effects (such as decreased serum T3 and T4) for iodine-sufficient adults. However, the size of this margin depends on a number of factors (dietary iodide intake, amount of iodide stored in the thyroid, and exposure duration), and is likely to vary among individuals in a population.

Fetuses and infants are likely to be more susceptible than healthy adults to the consequences of reduced thyroidal iodine uptake. A study of deceased preterm and term infants showed that their thyroids have only small stores of thyroxine in thyroglobulin (van den Hove *et al*., 1999). These authors found the turnover of the thyroxine pool of these maturing thyroids is 100 percent per day. Because of this high turnover, iodide depletion could rapidly lead to deficient thyroid hormone secretion. In a study of effects of marginal iodine deficiency in pregnant rats, Versloot *et al.* (1997) found that the maternal thyroid can compensate for low iodide availability by increasing its activity, whereas the fetal thyroid is not able to regulate its iodide metabolism, which resulted in a 50 percent decrease in thyroidal iodide uptake. This can lead to a lower fetal T4 production at a time when a normal T4 level is required for the normal development of many organs, especially the brain.

The size and variability of this implicit margin of safety seems an appropriate subject of further study, but OEHHA has seen no data that would substantiate the 50-100 fold safety margin claimed in the comment. In order to be protective of the sensitive subgroups that are marginally iodine deficient, OEHHA identifies the inhibition of iodine uptake as the critical endpoint in the development of the PHG.

Comment 2: "The application of an uncertainty factor of 10 for intraspecies variability: There is reason to believe that people with deficient iodine intake could be sensitive to environmental goitrogens and that pregnancy is a significant stress on the thyroid. However, thyroid function is normal during pregnancy in iodine sufficient or marginally

deficient people. Available data show that the U.S. population has adequate iodine intake and there is no evidence of an iodine deficient population in the U.S. There are powerful physiological regulatory mechanisms that protect against effects of moderate changes in iodine supply. In addition thyroid disease in the U.S. is primarily due to autoimmune disease and is not related to iodine status. Finally, the dose-response relationship of iodide uptake inhibition and perchlorate dose is known with little uncertainty."

Response 2: There is clearly a negative feedback system in regulating thyroid hormones. However, based on the available human studies, it is not clear what perchlorate exposure level would disrupt this system. Due to individual variation in dietary iodine intake and amount of iodide stored in the thyroid, the threshold of this disruption is probably highly variable.

An uncertainty factor of 10 is applied in the perchlorate risk assessment to account for the uncertainties in extrapolating from the Greer *et al.* (2002) study results to the general population and sensitive subgroups. There were only 37 volunteers in the study; the individual variability represented by the data is likely to be smaller than that in the general population. The volunteers were healthy adults; their iodide intake levels were relatively high during the study period. The Greer *et al*. study did not include the sensitive subgroups identified in the PHG, such as pregnant women with marginal iodide intake, infants, and individuals with impaired thyroid function.

Although safe exposure levels are customarily based on clear toxic effects rather than precursor effects, it is certainly less health-protective to rely on the compensatory mechanism of the body to counter the stress put on it by environmental contaminants. Furthermore, there are clinical data showing that pregnant women with marginal iodine deficiency are more likely to develop thyroid enlargement. In these cases, the thyroid system is already out of balance and any additional stress can be considered adverse.

The NHANES III data have been interpreted as showing that there is no iodine deficiency in the general population of the U.S. However, the NHANES III and NHANES I data also indicate that the median urinary iodide in women of childbearing age (15-44 years) has dropped significantly from 294 µg/L (1971-1974) to 128 µg/L (1988-1994) (Hollowell *et al*., 1998). The NHANES III data indicate the possibility that some pregnant and lactating women are getting less than the optimal amount of iodine from their diet.

There is reason to believe that a majority of hypothyroidism cases in the U.S. are due to autoimmune disease. However, the end result of the disease is a reduced capacity of the thyroid to produce thyroid hormones, thus causing hypothyroidism. It is possible that these patients are more susceptible to the thyroid-disrupting effects of perchlorate exposure.

Comment 3: "The uncertainty factor of 3 for duration and database deficiencies: The human clinical studies do not address chronic exposure. However, there is no accumulation of dose due to rapid clearance of perchlorate. There would be no accumulation of effect from short-term to chronic exposure duration in iodine sufficient populations. Occupational studies with chronic perchlorate doses in the same range as

the clinical study demonstrate normal thyroid hormone levels. The other database concerns mentioned in the PHG document are addressed in these comments, this uncertainty factor is not warranted."

Response 3: Based on the comments OEHHA received from the public and the reviewers of the second University of California peer review (OEHHA, 2004), OEHHA no longer applies an uncertainty factor of three to account for the short exposure duration in the Greer *et al*. (2002) study and the limitation of the database.

Comment 4: *The draft PHG document uses the most significant uncertainty, the potential sensitivity of pregnant women with low iodine intake, to justify labeling iodide uptake inhibition as adverse, with an inherent 50-100-fold safety margin, and as the basis for applying an uncertainty factor of 10 for intraspecies uncertainty and a factor of 3 for database/duration. The multiple counting of the most significant source of uncertainty is a logical error that results in a PHG that is unnecessarily low. Multiple considerations of the same uncertainty are not appropriate and should be changed.*

Response 4: In the final risk assessment, OEHHA applies an uncertainty factor of 10 to account for interindividual variability. There were only 37 volunteers in the Greer *et al*. (2002) study; the individual variability represented by the data is likely to be smaller than that in the general population. The volunteers were healthy adults; their iodide intake levels were relatively high during the study period. The Greer *et al*. study did not include the sensitive subgroups identified in the PHG, such as pregnant women and lactating women with marginal iodide intake, infants, and individuals with impaired thyroid function. For these reasons, OEHHA believes the use of this uncertainty factor is justified. As described in the responses to earlier comments, OEHHA eliminated the three-fold uncertainty factor in the final PHG.

Comment 5: "A logical dilemma in the draft PHG is the failure to maintain the distinction between qualitative associations and quantitative relationships. This is evident in the discussion of sensitive populations in which a series of logical connections are made to associate perchlorate-induced inhibition of iodine uptake to neurodevelopmental effects."

Response 5: OEHHA agrees that the relationships between many adverse health effects and severity of iodine deficiency are not well characterized in the studies reviewed for this risk assessment, but does not agree that there is any "logical dilemma" in assuming a dose-response relationship. Considering the uncertainty in characterizing the iodine deficiency syndromes, it is even more difficult to describe quantitatively the relationships between perchlorate dose and these adverse health effects. The difficulty is also compounded by the variability of iodine status, compensatory capacity of the thyroid, and exposure to other environmental goitrogens. This is one of the reasons why reduction in thyroidal iodide uptake was chosen as the critical endpoint for the development of the PHG.

Comment 6: "We disagree with the use of the phrase 'adverse effects associated with low-dose perchlorate exposure'. First, it is inappropriate to imply that there are adverse effects associated with low-dose perchlorate because the term 'low-dose' is not defined and the extent of iodine deficiency that it is being compared with is not defined. At some combination of perchlorate dose and degree of iodine deficiency this may be true, but not at all doses or iodine intake levels, so it must be specified. The potential for adverse effects and the dose at which they may occur are to be determined by the risk assessment and should not be stated as a foregone conclusion."

Response 6: OEHHA agrees that the nature and severity of health effects are related to the extent and duration of perchlorate exposure as well as the iodine status of the individual. The phrase in the PHG document, "many adverse health effects associated with low-dose perchlorate exposure are expected to be similar to those caused by iodine deficiency" is made to emphasize that at higher perchlorate doses other adverse health effects may occur (such as blood disorders) that are not related to the disruption of thyroid hormone homeostasis. The phrase is also used to summarize health-effect information gained from animal and human studies.

Comment 7: "The definition of iodide uptake inhibition as adverse is a significant deviation from basic principles of thyroidology and risk assessment, and must be justified. It contradicts the understanding of homeostatic mechanisms in general, and the well-known thyroid homeostasis over a very wide range of iodine and goitrogen nutritional status. If the inhibition is considered adverse because it is a precursor to subsequent, possibly adverse effects, or to account for iodine deficient populations, this should be clarified. It is a common practice to use precursor effects in a risk assessment when the dose-response relationships for the adverse effect is not known, as in this case, or when the quantitative difference between the effective doses for the precursor effect and the adverse effect is small or poorly defined, which is not the case for perchlorate. The thyroid has considerable ability to compensate for iodide uptake inhibition, and it takes much more to show clinical or adverse effects."

Response 7: Inhibition of iodide uptake makes a convenient, well-quantified, indicator of effect. It is clearly not a frank toxic effect, but nevertheless, the benchmark dose for lack of significant inhibition of iodide uptake in a human study is a valid risk assessment endpoint. Also, as iodine is an essential nutrient, any significant inhibition of its uptake, particularly in systems under stress, should be considered undesirable.

The thresholds for serum T4, TSH change, thyroid colloid depletion, and thyroid enlargement as a result of perchlorate exposure are much more affected by a number of highly variable parameters (such as dietary iodine intake, the amount of iodide stored in the thyroid, exposure duration, and pregnancy) than the inhibition of iodide uptake. Due to the insufficient control of one or more of the parameters, there are no human data available that allow the establishment of a dose-response relationship for these adverse health effects. OEHHA acknowledges there is probably a safety margin between the inhibition of iodide uptake and other more serious thyroid effects, although the magnitude of this margin is not well quantified and is likely to vary among individuals in

a population. We have attempted to discuss these issues more clearly in the final PHG document.

Comment 8: *Based on the clinical and occupational data available,* "approximate bounds can be estimated for the dose range that could cause an effect on thyroid hormones. Occupational studies show no effect on hormone levels in people exposed to 0.5 mg/kg/d or less [for a duration of 12 hours/day] over a 5-year working period. The dose used to control Grave's disease is 13 mg/kg/d, and a typical maintenance dose is 1.2 mg/kg/d. The lowest maintenance dose reported was 0.6 mg/kg/d, which could be considered as a NOAEL. The typical maintenance dose, 1.2 mg/kg/d, may be interpreted as a minimal LOAEL because it achieves the 'desired adverse effect' of altering hormone levels."

"These data support the conclusion that a dose of 0.5-0.6 mg/kg/d is expected to be a threshold level for changes in thyroid hormone homeostasis. The Greer data and the PBPK model suggest that iodide uptake inhibition would be 70% or more at this dose, so significant persistent inhibition of iodide uptake would not affect hormone homeostasis or cause subsequent adverse effects in an iodine sufficient population. This analysis leads to the conclusion that a safety margin between the precursor to the adverse effect (NOAEL) and the pharmacological effect (NOEL) is on the order of 40-100. None of these comparisons can lead to a clear conclusion about the magnitude of the inherent safety margin between the toxic effect and the pharmacological effect because the data on perchlorate induced hormone changes is too limited. However, each comparison suggests that the margin would be no less than the range of 50-100."

Response 8: The studies on Grave's disease refer to hyperthyroid individuals, so relevance to potential hormonal status in hypothyroid individuals is unclear. The occupational studies of Gibbs *et al.* (1998) and Lamm *et al*. (1999) are both cross-sectional studies. The extent of perchlorate exposure and the thyroid function parameters were quantified at a specific time only. Depending on the amount of iodide stored in the thyroid, it may take an extended period of time (weeks to months) before a partial inhibition of thyroidal iodide uptake would cause changes in serum thyroid or pituitary hormone levels. Furthermore, due to the intermittent nature of perchlorate exposure in the study reported by Lamm *et al.* (1999), there is considerable uncertainty in estimating the threshold for thyroidal iodide uptake inhibition. The threshold for hormonal changes in hypothyroid pregnant women and in infants cannot be determined from any of these data. Because of these limitations, the "safety margin" between the inhibition of iodide uptake and detectable hormonal effects may not be as high as 40-100, as suggested by the commenter.

Stanbury and Wyngaarden (1952) studied a group of patients with Graves' disease. They pretreated the patients with a drug that prevents oxidation of iodide ion and thyroid hormone synthesis and dosed them with a tracer of radioactive iodide. Following the treatment, different doses of potassium perchlorate ranging from 3-500 mg were given orally. They reported that a single oral dose of 10 mg caused about 50 percent release of accumulated iodine, and doses as low as 3 mg caused detectable release of iodide from the thyroid. While there are many limitations with the design of the study, the result

showed that a perchlorate dose as low as 31 µg/kg or 0.031 mg/kg (assuming a body weight of 70 kg) could cause discharge of iodide stored in the thyroid. This estimate challenges the assertion that "These data support the conclusion that a dose of 0.5-0.6 mg/kg/d is expected to be a threshold level for changes in thyroid hormone homeostasis."

Comment 9: "The PHG document also concludes that it is necessary to prevent a dose that causes iodide release (pg 72). However, it is not clear how the authors are interpreting iodine release in the perchlorate discharge test as it pertains to the risk assessment (Page 47 – para 4, discussion of Stanbury and Wyngaarden, 1952)." ... "A dose of 1,000 mg perchlorate is used in the test, and a 100 mg dose (1.4 mg/kg/d) has been shown to result in nearly complete discharge. A dose of 10 mg (0.14 mg/kg/d) results in substantial discharge (the Greer *et al.*, 2002, data predict over 50% inhibition at this dose). Stanbury and Wyngaarden, 1952, report that a 3 mg dose of KI caused a 'considerable fall' in thyroidal iodide, consistent with the prediction based on Greer *et al.* (2002), that the dose of 3 mg KI in drinking water would cause 25% inhibition of 24-hr iodide uptake. Iodide release in the perchlorate discharge test is not an adverse effect and further justification is required if the results of Stanbury and Wyngaarden (1952) are used to define the NOAEL of perchlorate."

Response 9: It is appropriate to keep perchlorate exposure below the threshold of iodide discharge from the thyroid. The iodide stored in the thyroid is used to maintain the normal production of thyroidal hormones when there is a transient decrease in iodide uptake. For this reason, a reduction of the iodide stored in the thyroid represents a decreased compensatory capacity of the body against other anti-thyroid agents and can be interpreted as an adverse effect. The human data reported by Stanbury and Wyngaarden, (1952) highlighted the multiple effects of perchlorate on the thyroid and the associated dose ranges.

As stated in the PHG document, a LOAEL was not identified for the study of Stanbury and Wyngaarden (1952) because: (a) exposure was acute, (b) the number of subjects in each dose group is not known, (c) the patients were pretreated with drugs that may enhance the release of thyroidal iodide by preventing the oxidation of iodide ion to iodine and thyroid hormone synthesis.

Comment 10: *Measurement of radioactive iodine uptake (RAIU)* "is a whole-body measure of multiple competing physiological processes, principally serum binding, glomerular filtration, urinary excretion, iodine uptake in the thyroid, and uptake in other tissues, over an 8- or 24-hour period. The RAIU is dependent on the dynamic pattern of perchlorate serum concentration superimposed on the labeled iodide serum levels. ... The variability of the RAIU measurement is compounded when the inhibition is calculated as the ratio of the treatment day to the baseline measure that was done over two weeks prior to the treatment measurement. All the variables...could vary substantially between the baseline RAIU and the treatment RAIU. These variables reflect intra-individual variability due to variables that cannot be controlled in a clinical study. These variables do not reflect inter-individual variability in the response to perchlorate."

"Clearly, there is some inter-individual variability in their response to perchlorate. It cannot be determined how much of the observed variation in the RAIU measurement is due to differences in sensitivity to perchlorate."

Response 10: OEHHA agrees; revisions in the document more clearly address this issue.

Comment 11: *The commenter suggested genetic variability in response to perchlorate is unknown, but unlikely to be large. It was argued that "*There are no significant genetic differences*" in the structure of NIS in humans, citing a 1998 paper by Spitzweg et al. Furthermore, it was argued that based on the Greer et al. (2002) data, perchlorate kinetic behavior also does not appear to vary substantially. The study data show that the serum half-time in eight subjects in the 0.5 mg/kg-day group ranged from 6-9.3 hours, with a mean of 8.1 hours.*

Response 11: The NIS structure is probably highly conserved in humans, although we are not aware of studies on genetic variability in human populations. This was not the focus of the Spitzweg study, although Spitzweg *et al.* (1998) mention that "Several hNIS gene mutations have been detected in patients with congenital hypothyroidism caused by an iodide transport defect," referring to three other studies on individuals, not populations. It is uncertain how representative the Greer *et al.* data are, especially considering the small sample size. In the development of the PHG, the uncertainty factor for interindividual variability also includes the effect of different exposure scenarios for different age groups.

Comment 12: *A preliminary analysis of the clinical study and a preliminary analysis based on the PBPK model have led to different conclusions regarding whether reduced iodine intake would change the extent of iodide uptake inhibition caused by perchlorate.*

Response 12: OEHHA agrees there is substantial uncertainty on this issue.

Comment 13: *The commenter disagrees with the concept that there are significant enough variations in iodine and dietary goitrogen intake to have any effect on thyroid status in the U.S. One of the reasons provided by the commenter is that there is universal iodination of salt in the U.S. and that there is stored iodide in the thyroid.*

Response 13: Iodizing of salt is voluntary in the U.S., and specialty salts such as Kosher salt and products sold as "sea salt" are not iodized. It is commonly estimated that only about 40 to 50 percent of salt consumed at home is iodized, and it should be noted that the majority of salt sold to food processors, including fast-food restaurants, is not iodized. Increased use of the specialty salt products, greater consumption of foods prepared outside the home, and a greater application of salt-restricted diets are presumably responsible for the decrease in urinary iodine levels between the NHANES I and NHANES III surveys. Also, smokers are likely to be exposed to more environmental goitrogens than non-smokers, because tobacco smoke is known to contain goitrogens (Knudsen *et al*., 2002). For all these reasons, OEHHA believes that the iodide status of

the population bears watching, and that a small proportion of the population may be at risk of inadequate iodine intake.

Comment 14: "[I]n the U.S., the primary cause of hypothyroidism is autoimmune thyroid disorders (Foley, 1992; Braverman and Utiger, 2000). Insufficient iodine is not a contributing factor in these diseases in an iodine sufficient population, and iodine supplementation is not used therapeutically. There is no evidence that the NIS is different in autoimmune thyroid disorders so the inhibition kinetics should not differ. It follows that, with adequate iodine nutrition, hypothyroid people would not be more sensitive to perchlorate than a person without hypothyroidism, so no additional uncertainty factor is necessary to protect this population."

Response 14: One of the results of autoimmune thyroid disorders is damage to thyroid tissues and reduction in thyroid hormone output. The reduction in the number of viable thyroid follicular cells and the amount of stored iodide may make this group of individuals more susceptible to the anti-thyroid effects of perchlorate.

Comment 15: "While it is clear that pregnancy causes changes in the thyroid gland, gestational and post-partum maternal thyroid changes are caused by a combination of factors (Glinoer *et al.*, 1990). The major factors, changes in TBG binding and hCG stimulation of the thyroid, are not related to iodine availability. Increased iodine losses to the urine and to the fetus also occur. To understand how these changes are related to perchlorate, two aspects of the discussion need to be clarified in the PHG draft. The normal changes in the thyroid during pregnancy (Burrow *et al*., 1994) should be distinguished from changes that are caused by iodine nutrition, and the draft PHG should consistently describe the extent of iodine deficiency in the studies that are cited to show the effects of pregnancy."

Response 15: In a review paper, Glinoer (2001) suggested that pregnancy itself is a stress on the thyroid system. When there is sufficient iodine supply, the thyroid can adapt to the many changes occurred during gestation. When there is insufficient iodine supply, pregnancy causes undesirable changes in the thyroid structure and thyroid hormone levels. In three prospective studies (Romano *et al.*, 1991; Pedersen *et al.*, 1993; Glinoer *et al.*, 1995), it was shown that iodide supplementation could reduce the stress on the thyroid during pregnancy.

OEHHA disagrees with the commenter that thyroid hormone changes and thyroid enlargement occur normally during pregnancy. Liberman *et al*. (1998), Long *et al*. (1985), and Levy *et al*. (1980) reported that pregnancy did not adversely affect thyroid function in iodide-replete populations.

Comment 16: "It is not clear whether these thyroid changes during pregnancy are relevant to perchlorate or whether they are adverse. Thus, these studies and many others illustrate a continuum on iodine deficiency effects with severe deficiency causing goiter, large TSH increases, T4 decreases outside of the normal range, and neurodevelopmental effects. In moderate to severe iodine deficiency thyroid size is increased and T4 is

decreased, with unlikely developmental effects because the fetus is protected by other mechanisms. In mild to moderate deficiency there are changes in thyroid size, and TSH, T4 and T3 change but remain within the normal range, increased total T4 and TBG, and no developmental effects. The US population falls into the iodine sufficient category, with minimal if any increase in thyroid size."

Response 16: A study reported by Rotondi *et al.* (2000) demonstrated that there may be a cumulative goitrogenic effect of successive pregnancies. They found that in women with moderate iodine deficiency (40-100 µg/day of urinary iodine), there is a statistically significant correlation between the number of completed pregnancies and thyroid volume. The result indicates that the goitrogenic effect of pregnancy may not be fully reversible, and therefore could be considered an undesirable effect.

OEHHA acknowledges that the dose-response relationships between a combination of perchlorate dose/iodine deficiency and adverse health effects related to thyroid function impairment have not been well characterized. The nature and severity of the effects are probably related to the severity of iodine deficiency and the degree of perchlorate exposure.

It is also true that the general population of the U.S. is iodine sufficient. However, the possibility that there is a group of individuals in California who are marginally iodine deficient (e.g., due to eating habits, exposure to other environmental goitrogens, or pregnancy) cannot be ruled out. Inhibition of iodide uptake into the thyroid by perchlorate in these individuals might well increase the severity of the iodine deficit and consequently the associated adverse health effects.

Comment 17: *The commenter suggested the correlation between adverse neurodevelopment and iodine deficiency in pregnant women reported by Pop et al. (1999) and Haddow et al. (1999) was weak. It was also suggested that many potentially confounding factors such as alcohol consumption, maternal depression, and negative life events were not adequately controlled.*

Response 17: From several studies cited in the PHG document, there is a strong association between severe or moderate iodine deficiency in pregnancy and impaired neurodevelopment. The importance of the study results reported by Pop *et al*. (1999) and Haddow *et al.* (1999) is that they indicate this type of effect can be extended to women with mild iodine deficiency as well. We agree that the associations are weaker with milder iodine deficiency, and that confounding factors are relevant. The recent association of smoking with iodine deficiency (Knudsen *et al.*, 2002; Laurberg *et al.*, 2004), for example, reveals a confounder that deserves further study.

Comment 18: "It is appropriate to identify pregnant women and their fetuses as the likely most sensitive population. There is information available that is pertinent to each of the factors mentioned in the PHG draft as a basis for the adoption of the intraspecies uncertainty factor.

- There is no evidence of a significant population in the U.S. with marginal iodine intake.
- Thyroid function is a preferable criterion over random urine samples for determining adequacy of iodine intake
- The literature shows that pregnancy changes the thyroid independent of iodine nutritional status.
- Larger effects on thyroid size are found in moderately iodine deficient pregnant women than in iodine sufficient women.
- Moderate iodine deficiency results in successful adaptation without effects on thyroid hormone homeostasis.
- Only in severe iodine deficiency is there a loss of thyroid hormone homeostasis.
- Some concern remains for a population such as strict vegetarians with high intake of a dietary goitrogen and not using iodized salt or processed food, but such a population has not been identified.
- The threshold for iodide uptake inhibition is not expected to vary across populations.
- The threshold for thyroidal iodine uptake inhibition is well-defined by the Greer *et al.*, 2002, study.
- The evidence that mild, asymptomatic maternal hypothyroidism leads to impaired neurodevelopment is not strongly supported.
- On an individual basis, there is minimal variability expected because the NIS is the same across individuals and in various organs.

Based on these cumulative considerations, an uncertainty factor of 3 for intraspecies variability appears to be adequate to protect public health."

Response 18: An uncertainty factor of 10 for interindividual variability for the estimate based on adult parameters has been retained in the final PHG document. OEHHA believes that a factor of three would not adequately account for all the individual factors, as well as the relatively high dietary iodine intake by the subjects in the Greer *et al.* (2002) study. Effects of perchlorate on the fetus must also be considered.

Individual variations in NIS have been reported (Spitzweg *et al.*, 1998), and the population distribution of the various forms is unknown.

Comment 19: "Perchlorate is one of the best-studied chemicals, from a toxicological perspective, in existence. It has been through two rounds of peer-directed research focused specifically on data needs for risk assessment. It has a well-described mechanism of action. Toxicological studies of perchlorate include developmental studies in two species, a multigeneration reproductive study, a rodent cancer study, mutagenicity studies, and subchronic studies in animals. There is a long history of clinical use and two high-quality clinical studies that define the dose-response relationship for the critical effect. In addition, there are two occupational studies, and an epidemiological study, in highly exposed populations. Finally there are several ecological epidemiological studies of people exposed to very low concentration in the U.S. that have found no effects.

There is no reliable evidence of any adverse effect that is not mediated by inhibition of thyroidal iodide transport. There is a clear understanding of the expected effects because of the vast literature on iodine deficiency disorders. This chemical has a nearly ideal database for risk assessment and minimal uncertainty." *The commenter suggested that the uncertainty factor of three for the limitation of the database is therefore unwarranted.*

Response 19: The statement that "There is no reliable evidence of any adverse effect that is not mediated by inhibition of thyroidal iodide transport" is not true. From clinical reports, there are documented cases of skin rashes, gastrointestinal irritation, and serious blood disorders that resulted from the ingestion of high doses of perchlorate. These disorders are not believed to be related to the disruption of thyroid hormone balance.

Based on the recommendations of the reviewers of the second University of California peer review (OEHHA, 2004), OEHHA no longer applies a three-fold uncertainty factor for short exposure duration in the Greer *et al*. (2002) study and database limitation in the final perchlorate PHG document.

Comment 20: "Clearly the designation of adversity of iodide uptake inhibition, the designation of the NOAEL, the duration of exposure, and sensitive populations are interrelated. However, the quantitative consideration of these issues should be performed as independently as possible to avoid insurmountable complexities. The sensitivity of people with marginal iodine intake, pregnancy, or thyroid disease, are appropriately addressed in the context of the intraspecies uncertainty analysis, and the determination of an effect level should consider the mechanism of action independent of the sensitive populations. Likewise, consideration of uncertainty due to duration of exposure should reflect knowledge of the accumulation of effects and dose, and not the role of sensitive populations. The current draft proposes an unnecessarily low PHG because multiple quantitative decisions are supported with similar or overlapping concerns, resulting in inflation of the perceived uncertainty beyond what is necessary based on the data."

"The evidence shows that neurodevelopmental effects are not known to be related to slight changes in thyroid hormones, that a dramatic reduction in iodine intake is required to affect thyroid hormone balance, considerably beyond the levels that cause thyroid enlargement, and that there is no substantial iodine deficient population in the US. The data further indicate that a considerable amount of sustained inhibition of iodide uptake by an inhibitor like perchlorate would be required to result in thyroid hormone changes that could lead to developmental effects. Therefore, a risk assessment based on inhibition of iodide uptake has a considerable inherent safety margin because inhibition is not adverse. It is imperative to the scientific credibility of the OEHHA risk assessment that this distinction be made and considered in the subsequent determination of the appropriate uncertainty factor."

"The OEHHA draft PHG addresses the uncertainties in a somewhat incomplete way, and substitutes extra adjustments for uncertainties when there are data available that address many of the uncertainties. Based on additional information presented in these comments and in other public comments, the draft PHG appears to by overly conservative by a factor of 50-100."

Response 20: OEHHA believes that the use of an uncertainty factor of 10 to extrapolate results from the Greer *et al*. (2002) study to the general population is appropriate. Other commenters have commented that it is not large enough. OEHHA agrees with the commenter that there is an additional unquantified safety margin between the reversible inhibition of iodine uptake by perchlorate and induction of hypothyroidism or neurodevelopmental effects. However, the variability within the population and the resulting potential for such effects has not been well addressed by the available data. OEHHA believes that the goal of protection of the population from potential effects of a drinking water contaminant with no beneficial purpose in the water would not be served by setting the PHG at a level that is likely to have widespread effects.

Comments from Arnold Engel and Steven H. Lamm

Comment 1: *Using the NHANES III database, the commenters presented an analysis showing a lack of correlation between cigarette smoking and serum T4 and TSH levels in individuals with low iodine excretion (<50 µg/L). They argued that by analogy, exposure to perchlorate is unlikely to have a synergistic effect on low iodine levels.*

Response 1: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types.

Comments from Amy Kyle, U.C. Berkeley, at the Perchlorate Workshop

Comment 1: *Why is there no uncertainty factor to account for using experimental results with a short time frame and applying them to a much longer time frame? Generally, there is an uncertainty factor of 10 even to go from subchronic to chronic. In this case, the draft risk assessment on perchlorate is going almost from acute to lifetime, yet there is no uncertainty factor for that.*

Response 1: No uncertainty factor has been used to specifically compensate for the short-term study because the nature of the endpoint (i.e., inhibition of iodide uptake into the thyroid) does not require one. Inhibition of iodide uptake represents an early step in the chain of events that can lead to impairment of thyroid functions and other related health effects. NIS inhibition by perchlorate is believed to be a phenomenon with a threshold, and when perchlorate exposure is kept at or below the threshold, there is no reduction in thyroidal iodide uptake. In other words, under such circumstances, the thyroidal iodide uptake is normal.

In the study of Greer *et al.* (2002), the inhibition of thyroid iodide uptake did not worsen over a 14-day period. The inhibition was also found to be completely reversible, which is consistent with other data. Based on the information available on animal and human absorption and excretion of perchlorate, there is little accumulated in the body. There are some animal data indicating the thyroid gland may accumulate a higher concentration of perchlorate than other body tissues, but perchlorate has a relatively short biological half-life in humans, approximately eight hours. For all these reasons, increasing duration of perchlorate exposure at doses below the threshold is not likely to increase the risk of thyroid disorders.

Comment 2: *Even if the inhibition of thyroidal NIS is reversible, effects on fetuses and children may not be reversible. Also there seem to be some time issues related to whether there is storage of some of the intermediates in the body. It seems unlikely that 14 days is sufficient to understand what happens to the intermediates. Also, some of your own data suggest that there were some effects manifested at 90 days in animal studies that were not manifested at 14 days.*

Response 2: The goal of the PHG is to prevent the occurrence of the first step in the chain of events that ultimately could lead to impairment of thyroid functions and other related health effects (including the potential adverse health effects on fetuses and children). It is reasoned that by setting a dose level that is below the threshold of the first step, all subsequent health effects and risks can be avoided.

If daily perchlorate doses are higher than the threshold of thyroidal NIS inhibition, then increasing the exposure duration may bring out more adverse health effects, as in the animal studies referred to above. The animal data mentioned by the commenter are related to thyroid impairment, such as depletion of stored colloid. Depletion of thyroidal iodide colloid stores is a gradual process. Conversely, daily doses below the threshold will not deplete iodine from the thyroid.

It is not clear what kind of "intermediates" the commenter was referring to. OEHHA is not aware of health effects associated with metabolites of perchlorate.

Comments from John Gaston at the Perchlorate Workshop

Comment 1: *The commenter questioned the use of 60 percent for the relative source contribution, observing that it is not clear where the other 40 percent might come from.*

The accumulation of perchlorate by lettuce doesn't establish a credible exposure pathway.

Response 1: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food.

Comments from Renee Sharp, Environmental Working Group, at the Perchlorate Workshop

Comment 1: *Why is it that when U.S. EPA evaluated the Greer et al. (2002) study, they determined that the lowest dose is the LOAEL and when OEHHA evaluated the same data set, OEHHA determined that the lowest dose is a NOAEL?*

Response 1: The PHG has been revised. Instead of using the LOAEL/NOAEL approach, OEHHA now uses a benchmark dose approach in evaluating the human data reported by Greer *et al.* (2002). A five percent inhibition of uptake is identified as the point of departure, and the lower 95 percent confidence level of the point of departure is used as the basis for PHG development. The benchmark dose calculation was done in consultation with U.S. EPA personnel, using the U.S. EPA benchmark dose software. This approach uses all the Greer *et al*. (2002) study data, and avoids the problem of low statistical power of the lowest dose, for estimation of a NOAEL or LOAEL.

Comment 2: *The commenter suggested that chronic effects of low perchlorate doses on humans, concentration of perchlorate in breast milk, sensitivity of the infant thyroid, individual variability, and diffusion of iodide out of the thyroid caused by perchlorate are some of the uncertainties, and an uncertainty factor of 30 is "almost unprecedentedly low" and not sufficient to cover them.*

Response 2: OEHHA believes that by using inhibition of iodide uptake as the critical endpoint, an uncertainty factor of 10 is sufficient to protect the sensitive subpopulations as well as the general population. It is important to note that this is assuming any adverse health effects of chronic perchlorate exposure are related to the anti-thyroid effects of

perchlorate. At this time, OEHHA is not aware of any demonstrated adverse effects of low-dose perchlorate that are not related to thyroid hormone disruption.

As discussed in the PHG, an acute oral dose of perchlorate (3-500 mg) was reported to cause discharge of stored thyroidal iodide in patients treated with 1-methyl-2-mercaptoimidazole (Stanbury and Wyngaarden, 1952). It was found that doses over 100 mg caused almost complete discharge and a 3 mg dose also produced a considerable fall in thyroidal iodide. This LOAEL of 3 mg is roughly equivalent to 0.031 mg perchlorate/kg-day, assuming an adult body weight of 70 kg. The administration of 1-methyl-2-mercaptoimidazole prior to the perchlorate dose was used to prevent the oxidation of iodide ion to iodine and thyroid hormone synthesis, and it might have increased the susceptibility of the thyroid to the iodide discharging effect of perchlorate. This theory is supported by the fact that a patient treated with propylthiouracil instead of 1-methyl-2-mercaptoimidazole did not have a discharge of thyroidal iodide when challenged with an acute oral dose of perchlorate.

Even assuming the general population is as sensitive as the patients who received 1-methyl-2-mercaptoimidazole and ignoring the dose-rate effect, the benchmark dose of 0.0037 mg/kg-day determined in the perchlorate risk assessment is approximately one-tenth of the LOAEL of 0.031 mg/kg-day. The margin of exposure from this transient effect level is more than 100, when an uncertainty factor of 10 is included. OEHHA believes the perhaps modest uncertainty factor of 10 in the final risk assessment is justified by the use of a sensitive "precursor" effect as the critical endpoint in an acceptable human study. OEHHA reduced the overall uncertainty factor to 10 because of the nature of this endpoint as well as the comments from the second University of California peer review (OEHHA, 2004).

Comment 3: *In order to meet the PHG mandates, the commenter suggested that the Lawrence (2000, 2001) studies must not be used in deriving the PHG, and infant body weight and drinking water consumption rate should be used rather than adult values in the PHG calculations, and concluded,* "In summary, given the serious and irreversible nature of the effects, the large areas [of] uncertainties remaining, the sensitivity of the population at risk, and the shortcoming of existing studies used to develop a PHG, the Perchlorate Action Group urges OEHHA to lower the public health goal for perchlorate to adequately protect the health of California's infants; the PHG should be no higher than 0.1 ppb." *This figure results from not using the Lawrence studies, increasing the combined uncertainty factor to 300, and using bottle-fed infant body weight and drinking water consumption values.*

Response 3: In the final risk assessment, the Lawrence *et al.* data (2000, 2001) were discussed, but only the human data reported by Greer *et al*. (2002) were used in the benchmark dose calculation to develop the perchlorate PHG.

In the PBPK work published by Clewell *et al*. (2003), they estimated that the serum perchlorate dose of the neonate rat fed on the milk of a perchlorate-exposed dam is lower than that of the lactating rat as well as the pregnant rat. In terms of inhibition of thyroid iodide uptake, Clewell *et al*. (2003) predicted that the fetal rat is the most sensitive subgroup at low doses (0.01–0.1 mg/kg-day), compared with the male rat, the pregnant

rat, and the lactating rat. While there could be interspecies differences in the absorption, distribution, and excretion of perchlorate, this modeling result indicates that the effective systemic dose of infants is similar to that of the nursing mother.

Also, in the document, exposure scenarios for infants and pregnant women were evaluated. OEHHA believes as discussed earlier in response to other commenters, that a combined uncertainty factor of 10 applied to calculations for pregnant women is adequate for extrapolation from the chosen endpoint.

Comments from Dan Guth, Boeing Corp, at the Perchlorate Workshop

Comment 1: *The commenter asked OEHHA to independently evaluate the recent animal toxicity data and not to totally rely on U.S. EPA's conclusions. It was suggested that the animal neurodevelopmental studies, the studies of brain morphometry and behavior, are inconclusive.*

Response 1: It is not possible for OEHHA to devote the level of effort needed to match U.S. EPA's exhaustive data evaluation and review process. We rely on U.S. EPA's evaluation of animal toxicity data, where appropriate. On the other hand, OEHHA did evaluate both the animal and human data, and our PHG is primarily based on the sensitive and relevant human data, while U.S. EPA has focused primarily on the animal data. The final document has been revised to indicate the level of our review effort of the animal data.

Comment 2: *The relatively large variability in the percentage reduction in thyroidal iodide uptake data reported by Greer et al. (2002) can be explained by the variability in dietary iodide intake and the variability in urinary excretion rate. So most of the variability in the data is actually intra-individual variability, variability within a person from day to day and hour to hour. Inter-individual variability may play a relatively minor role.*

Response 2: The discussion of interindividual variability has been revised in the final document to acknowledge this factor more clearly. Although we did not quantitatively estimate interindividual variability in susceptibility to the effect of perchlorate, we do not agree that it should be assumed to play a minor role.

Comments from Rick Pleus, Intertox Corp, at the Perchlorate Workshop

Comment 1: *The commenter believed that the inhibition of iodine uptake should be identified as a no-observed-effect level rather than as a NOAEL, i.e. as a precursor to an adverse effect rather than as an adverse effect, and concluded,* "If you translate that level into a safe drinking water level for an adult, you're about 180 to 200 parts per billion, and inherent in that are a whole set of conservative safety factors from the standpoint that you're looking at a precursor of a precursor of the possibility of an adverse health effect."

Response 1: OEHHA agrees that there is a buffer or safety margin between the inhibition of thyroidal iodine uptake and frank health effects. However, the magnitude of the buffer or safety margin is likely to vary from individual to individual depending on: dietary iodide intake, amount of iodide stored in the thyroid, exposure to other environmental goitrogens, and the capacity of the body in maintaining the thyroid hormone balance. At this time, there are no data allowing the characterization of this margin of safety in a population, including sensitive subgroups like fetuses and neonates. In order to protect this sensitive population, the effect on thyroidal NIS, measured by iodine uptake inhibition, was identified as the critical effect.

Comments from Jonathan Borak, Department of Medicine and Epidemiology, Yale University, on behalf of Lockheed-Martin, at the Perchlorate Workshop

Comment 1: *The commenter stated that he does not disagree with looking at the inhibition of iodine uptake as a critical key effect, but thinks it is misleading and a mistake to assume that it is the critical adverse effect. The dose range between that point which inhibits iodine uptake and those doses that perturb thyroid function is essentially a margin of safety that has been ignored for the purposes of the calculation.*

Response 1: OEHHA agrees that there is likely a buffer or safety margin between the inhibition of iodine uptake and other undesirable or adverse effects. However, the magnitude of the buffer or safety margin is likely to vary from individual to individual depending on: dietary iodide intake, amount of iodide stored in the thyroid, exposure to other environmental goitrogens, and the capacity of the body to maintain the thyroid hormone balance. At this time, there are no data allowing the characterization of this margin of safety in a population. In order to protect the sensitive population, including fetuses and neonates, the inhibition of thyroidal NIS and resulting inhibition of iodine uptake was identified as the critical effect. Because of the nature of the critical endpoint identified, OEHHA only applied an overall uncertainty factor of 10 in the final risk assessment.

Comment 2: "There is a statement...in the draft [that] reads, "recently a number of studies indicate that even mild to moderate iodine deficiency can reduce maternal serum thyroid hormone levels and impair the brain development in the offspring." That particular statement has eight specific references. ... My reading of the references...is that that statement is not supported by the references cited in the draft."

Response 2: The statement has been changed to "even less than severe iodine deficiency …" The references have also been modified in the revised document. OEHHA agrees that many of the studies cited have limitations: some of the subjects in the studies cited were suffering from various degrees of hypothyroidism or hypothyroxinemia and some studies did not measure iodine status or serum T4 level of the subjects. However, OEHHA believes that these studies are relevant to the issue of potential adverse health effects related to perchlorate exposure. The study results show that under certain

conditions, iodide deficiency and possibly exposure to perchlorate may lead to adverse neurodevelopment in fetuses and thyroid enlargement in pregnant women.

Comment 3: *Is there reason to believe ambient levels of perchlorate exposure would cause clinical hypothyroidism, demonstrable hypothyroidism, demonstrable in the laboratory or otherwise?*

Response 3: OEHHA agrees that the nature and severity of health effects are related to the extent and duration of perchlorate exposure as well as the iodine status of the individual. According to our modeling of the Greer *et al*. data, the equivalent drinking water level that corresponds to minimal NIS inhibition in iodide-sufficient adults is approximately 130 ppb, using default exposure parameters and no other sources of exposure.

Compared to this minimal effect level (in the study population), it is not clear what should be defined as the "ambient level" of perchlorate in drinking water. Exposures to perchlorate in the U.S. have varied over a wide range, and some effects have been claimed, with variable degrees of confidence. However, it appears to us that the exposure levels, the number of people exposed, and the exposure duration have not been adequate to expect clearly observable changes in the parameters measured. In our opinion, consideration of human variability, other sources of perchlorate exposure, and protection of sensitive subpopulations requires setting a health-protective level considerably below the level that would result in clinically observable effects.

Comment 4: *The relative source contribution of 60 percent is supported by a U.S. EPA study that is of questionable relevance. The study involved the growing of lettuce in greenhouse with sand, not soil, no attempt to emulate any growing area, irrigated with distilled water to which perchlorate was added, with no other competing anions. The critical issue is that perchlorate and chlorate are believed to be taken up by a nitrate-sensitive transport system, mainly passively, but competitively with all of the other anions in the irrigation water. In a real world situation, irrigation water is laden with other anions that would have competed with perchlorate anion for plant uptake.*

Response 4: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA

believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types.

Comment 5: *One can show that severe thyroid disturbances have adverse health effects, but I do not believe that one can show that mild disturbances within the normal range have such effects. This constitutes a significant data gap, and also an extra margin of safety that you're not stating in the risk assessment.*

Response 5: OEHHA agrees with the commenter that there are data gaps and it is difficult to identify the thresholds for various adverse health effects related to iodine deficiency. OEHHA also agrees that there should be an additional margin of safety between inhibition of iodine uptake into the thyroid and impairment of thyroid functions. However, the available data are insufficient to document its magnitude, particularly for potentially sensitive individuals such as fetuses and neonates. Additional clarification of this margin of safety has been added to the document, particularly in the Risk Characterization section.

Comments from Steven Lamm, medical consultant to a perchlorate manufacturer, at the Perchlorate Workshop

Comment 1: *Referring to IQ of children exposed to perchlorate, the commenter pointed out that in Nevada the fourth-grade school scores of children in an area exposed to perchlorate were not different from other areas. The level of exposure experienced by these children was twice the standard (6 ppb) that is being proposed.*

Response 1: OEHHA has not seen the study mentioned by the commenter, and is willing to review and consider the data when they are published.

Comments on the Second Public Release Draft

University of California peer reviewer #1

Comment 1: "Perchlorate like other chemicals absorbed in sufficient amounts into the circulation (including nitrate, chlorate, bromate, fluborate, thiocyanate, chloride, bromide, iodide, and other anions) can cause a transient decrease in synthesis and secretion of thyroid hormone synthesis and a compensatory increase in TSH (Capen, 1997). These chemicals are not new to human environments and they may act additively, synergistically or not at all on thyroid function. The possibility has not been adequately considered."

Response 1: A discussion of the existence of many chemicals in the environment that may affect the uptake of iodide into the thyroid and the production of thyroid hormones

in the thyroid has been added to the perchlorate risk assessment. A quantitative evaluation regarding the interactive effects of these environmental goitrogens and perchlorate is not possible at this time, due to the lack of potency and exposure data. However, PHGs (and MCLs) are or will be provided for several of these compounds (nitrate, chlorate, and bromate), which provides an additional means to limit total exposures to iodide uptake-inhibiting chemicals.

Comment 2: *The reviewer cited some preliminary unpublished data showing that perchlorate in lettuce (with an average of 28 ppb) produced in the Colorado River Valley yielded a potential dosage of 0.02 µg/kg-day. The data were also provided in Tables 1 and 2 of the comments.*

Response 2: The reviewer arrived at this result by using data from a relatively small study (24 samples) and by assuming lettuce is the only contaminated produce consumed. Recently, it has been shown that farm produce such as blackberries, strawberries, and cucumbers (Smith and Jackson, 2003) as well as dairy milk (Erickson, 2003; Kirk *et al.*, 2003) can also be contaminated with perchlorate. Combined exposures to contaminated products could therefore be much higher than estimated by the reviewer, although comprehensive sampling of foods has not yet been performed, and estimation of total dose is not yet possible. However, if we assume that all green leafy vegetables are contaminated at the same 28 ppb level, an average perchlorate dose of 0.08 µg/kg-day would result at the average consumption level for green leafy vegetables of 2.9 g/kg-day (OEHHA, 2000).

Comment 3: "Preliminary perchlorate analyses reveal that the nitrate:perchlorate ratio in lettuce is about 7,300:1 (mole ratio)… Most importantly the nitrate:perchlorate ratio urges caution in the assignment of biological or toxicological significance to ingestion of trace levels of perchlorate or any other NIS inhibitor in food or water. This issue may be critical to establishment of a PHG."

Response 3: A discussion of nitrate as a NIS inhibitor has been added to the perchlorate risk assessment. OEHHA believes that the presence of other goitrogens in the environment suggests a larger uncertainty factor or a lower RSC may be warranted in the perchlorate risk assessment. Further study of the competitive effect of nitrate will be required, although OEHHA has no reason at this time to presume that there is a significant risk to thyroid function from environmental exposures to nitrate (Lambers *et al.*, 2000). OEHHA has developed a PHG for nitrate; if new data suggest the nitrate PHG is inadequate for health protection, the PHG level will be reconsidered.

Comment 4: "Consideration of other sources of NIS inhibition including nitrate and thiocyanate should occur under the charge to OEHHA "to consider possible synergistic effects." For example, thiocyanates derived from cassava *Manihot esculenta* (a valuable starch source consumed by millions of people) and cigarette smoking are important in the etiology of human thyroid disease in iodine deficient population. There is also a substantial literature on laboratory and accidental animal poisoning by both nitrate and

thiocyanate (see Kingsbury, *Poisonous Plants of the United States and Canad*a, 1964) that is relevant to NIS inhibitor exposure. Given the lack of widespread thyroid disease in California, such a review could considerably inform OEHHA scientists of the significance of naturally-occurring iodine uptake inhibitors including nitrate and thiocyanate. The potential for interactions including synergism and antagonism has not been adequately explored. Recognition of the occurrence of NIS inhibitors and of possible interactions is of importance for risk assessment and risk communication."

Response 4: A discussion of the existence of many chemicals in the environment that may affect the uptake of iodide into the thyroid and the production of thyroid hormones in the thyroid has been added to the perchlorate risk assessment. OEHHA agrees that chronic exposures to environmental goitrogens may affect the health of the thyroid of those individuals that are getting less than the optimal amount of iodine from the diet. Due to the lack of potency and exposure data, a quantitative evaluation of the overall effect of exposure to a mixture of the environmental goitrogens is not possible at this time, although it is clear that perchlorate is the most potent of these chemicals.

Comment 5: "Dosages used to treat Graves' Disease are vastly greater than perchlorate levels that occur in drinking water. To acquire a dosage of 10 to 20 mg/kg-day, a 70 kg person would have to consume over 100,000 liters of water in one day, a useful point for risk communication with a wary public. Citation of such a dose in the context of determining a PHG serves to document the safety of trace levels of perchlorate exposure."

Response 5: Comparing the perchlorate dose used to treat Graves' Disease to ambient levels of perchlorate in water would not demonstrate the safety of current levels of perchlorate in water. The perchlorate dose required to treat patients with an overactive thyroid is certainly much greater than the dose that might affect sensitive populations, including pregnant women and infants who may be consuming diets with minimal iodine levels. The dose range (10 to 20 mg/kg-day) suggested by the reviewer for comparison is intended to have a frank effect on overactive thyroid function. Our risk assessment attempts to address persons with normal or hypoactive thyroids, and extrapolate downward from the frank effect levels to the level expected to prevent effects, even in sensitive populations. We hope that the dose-response evaluation and public health protective goal are clear in our discussion in the PHG document.

Comment 6: "Utilization of worker experience in risk assessment provides investigators opportunity to study higher-level exposures than occur in the general public. Capture and utilization of these real time dosage-response data should be given great importance in public health decision-making."

Response 6: Some of the occupational study results suggest that relatively high intermittent doses do not cause thyroid hormone imbalance in healthy workers, or any other adverse effects. However, the number of subjects in these studies is relatively small, the endpoints investigated are limited, and the intermittent nature of the exposures may mitigate potential effects.

Comment 7: "Relative Source Contribution (RSC) for drinking water will likely be larger than the default 80%. Other sources of perchlorate exposure including diet are very limited, and the potential RSC for produce, in particular, is minimal relative to water. If a higher perchlorate exposure level (BMDL) associated with an adverse effect is adopted for regulatory purposes the RSC will also be increased. … Based upon available preliminary data the RSC is likely to require adjustment (Krieger and Sanchez, Table 3)."

Response 7: The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al*., 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food.

The combined contribution of farm produce and dairy milk to the total perchlorate dose could easily be higher than that estimated by the reviewer (see response to comment 2), so that the RSC should be lowered, not increased. Using the estimated daily dose of 0.08 μg/kg-day estimated in response 2 from consumption of green leafy vegetables, with the perchlorate in water exposure in the reviewer's Table 3, the relative source contribution from the water would be 60 percent (0.6).

Comment 8: "There is no data to indicate that human exposures defined by single-digit perchlorate levels in water yield adverse health effects in humans. What data exist concerning the prevalence of iodine deficiency in California? The OEHHA Draft does not establish whether an iodine-deficient sensitive subpopulation exists."

Response 8: OEHHA agrees that there is little or no data showing there is iodine deficiency in California, on a population basis. One of the goals of the perchlorate PHG is to protect pregnant women and infants. Comments from the second University of California reviewers #2 and #3 (see below) support OEHHA's position on this issue.

Comment 9: "Discussion of the variability of urinary iodine levels provides foundation for acknowledgement of the plasticity of human utilization and excretion of iodine. Diurnal variation of urinary iodide (Rasmussen *et al.*, 1999) and day-to-day variation have been documented (Vought *et al.*, 1963; Rasmussen *et al.*, 1999)."

Response 9: It is important to note that the concern here is not the daily variation of thyroidal iodide uptake; the concern is the reduction in the weekly or monthly average thyroidal iodide uptake resulting from a continuous exposure to perchlorate in drinking water. No change to the risk assessment was made.

Comment 10: *The reviewer disagrees with the identification of the inhibition of NIS as an adverse effect. However, the reviewer still suggests the use of this end-point for dose-response evaluation. The reviewer concluded,* "Given these data, Greer *et al.* (2002) suggested the "true no effect level" for iodide uptake inhibition was 0.0052 mg/kg-day to 0.0064 mg/kg-day. These dosages would be equivalent to 180 ppb to 220 ppb perchlorate in the drinking water of a 70 kg person."

Response 10: Terms like adverse effect may have different meanings to different people. In order to minimize this potential for misunderstanding, OEHHA has altered the discussion of inhibition of NIS and iodine uptake in the perchlorate PHG document to refer to "critical effect," where applicable. A drinking water level of 180 ppb to 220 ppb implies an uncertainty factor of one, based on exposure of an adult. We are required to also protect sensitive subpopulations, including pregnant women, their fetuses, and infants. Comments from many external reviewers and those from the second University of California reviewers #2 and #3 support the use of an uncertainty factor greater than one to protect sensitive subpopulations.

Comment 11: "Inhibition of iodine uptake of up to 70% does not reduce T4 levels, even following prolonged exposures (Greer *et al.*, 2002). Clinical studies have shown 50% inhibition of iodine uptake with no effects on T4 or TSH (Abbassi, 2002). On that basis the critical effect of perchlorate exposure is not inhibition of iodine entry, but T4 decrease during pregnancy."

Response 11: OEHHA agrees that T4 decrease during pregnancy must be prevented. However, OEHHA does not agree with the statement, "Inhibition of iodine uptake of up to 70% does not reduce T4 levels, even following prolonged exposures." The healthy adult subjects in the Greer *et al.* study were only exposed for 14 days, which is far too short a time to deplete thyroid colloid stores, if there were a minimal negative iodine balance. Based on the baseline urinary iodine data provided by Goodman (2003) for the subjects in the Greer *et al.* study, the subjects were iodine sufficient at the time of the study. For these reasons, OEHHA does not believe the design of the study supports easy conclusions about the perchlorate dose needed to decrease serum T4 in all populations, especially pregnant women, the fetuses, and infants.

Comment 12: "Given that there is no public health emergency and that the U. S. EPA (2002) document is an External Review Draft, I am concerned about whether the Draft document represents the most complete scientific review that OEHHA can muster."

Response 12: OEHHA believes that the data available are adequate to reach a conclusion as to a public-health protective level of perchlorate in drinking water. The U.S. EPA evaluations are an important contribution, but are not the basis of the OEHHA risk

assessment. OEHHA has received many comments about the urgent need for a perchlorate PHG, and was mandated by state law (HSC §116293(a)) to adopt a perchlorate PHG by January 1, 2003. Although this deadline was not met due to a lawsuit, OEHHA is proceeding as directed by the resulting court order to publish the PHG within 60 days of receipt of the final peer review comments.

Comment 13: "Dozens of citations of U.S. EPA (2002) are included in the Draft. The U.S. EPA (2002) document is an External Review Draft (hence peer review not complete). The document was relied upon for much of the material presented in the Draft Public Health Goal for Perchlorate In Drinking Water. The results of the External Review of U. S. EPA (2002) are apparently not available to OEHHA and citations provided in the Draft do not give any indication of OEHHA review of the original data."

Response 13: Since the release of the second public review draft, OEHHA obtained additional data on the animal studies and the comments from the external review of the U.S. EPA (2002) perchlorate risk assessment. The PHG risk assessment has been modified to reflect the additional review of original studies, and our further evaluations. It is also important to know that OEHHA's final PHG determination is based on human data, and not on the conclusions of the U.S. EPA risk assessment.

Comment 14: "It seems reasonable to assume that important in-depth scientific review of U. S. EPA (2002) will be provided by the National Academy of Sciences' Committee to Assess the Health Implications of Perchlorate Ingestion. The Committee's work began in June 2003 and their report is due 15 months later. ... The current deliberations of the NAS Committee seem to be critically important to the decision-making process given the important role of U. S. EPA reviews in the OEHHA Draft. Lacking precise knowledge of the breadth of the University of California-managed review, the above issues may or may not be important concerns."

Response 14: The draft perchlorate PHG has gone through two external peer reviews, two public reviews, one public workshop, and three reviews by the U.S. EPA. OEHHA believes that state law and the superior court order require us to expeditiously develop a PHG. The PHG statute acknowledges the evolving nature of scientific knowledge, and mandates a review cycle (HSC §116365(e)(1)). The National Academy of Sciences (NAS) is conducting an evaluation of U.S. EPA's 2002 Draft Toxicological and Risk Characterization for Perchlorate. This is an important undertaking that may help guide efforts to study the health effects of perchlorate. When that evaluation is completed, OEHHA will carefully review the NAS conclusions and will revise the PHG as necessary (Health and Safety code section 116365(e)(1)).

University of California peer reviewer #2

Comment 1: *The reviewer agrees with OEHHA that the 2002 Greer et al. study is the most appropriate for establishing the dose-response relationship between perchlorate*

and inhibition of iodine uptake. The reviewer noted that the study has two limitations: "One of the primary disadvantages of using the Greer *et al.* study is the somewhat small sample size and low study power, although the size of this study is certainly comparable to many similar clinical investigations in humans. Another disadvantage of using this study is the need to extrapolate findings or add uncertainty factors to account for differences in susceptibility between healthy adults and potentially susceptible subpopulations. In my opinion, the advantages discussed above outweigh these disadvantages."

Response 1: OEHHA has acknowledged the shortcomings of the Greer *et al.* (2002) study in terms of establishing the dose-response relationship between perchlorate and inhibition of iodine uptake. Benchmark dose modeling and uncertainty factors are used in the evaluation to compensate for the limitations discussed.

Comment 2: *Referring to the available epidemiology studies, the reviewer noted,* "Given the use of ecological exposure data, the large potential for exposure misclassification, and the relatively low levels of exposure, the negative findings in this study and similar investigations add little to our knowledge of perchlorate. ... The findings of the two low-dose population studies that did identify effects are also difficult to interpret. Questions have been raised about bias relating to the timing of thyroid testing and control for ethnicity in the Brechner *et al.* study (1, 14). The Schwartz study identified effects on T4 at exposures greater than 13 ppb and a possible dose response relationship at lower doses (13). This study is also not conclusive given the ecological exposure analyses and possible confounding."

Response 2: OEHHA agrees with the reviewer. OEHHA finds the ecological study results informative but we do not believe they are suitable for dose-response characterization.

Comment 3: "Several occupational studies have also failed to identify links between perchlorate and potential health effects (17, 18). These studies provide some reassurance that occupational perchlorate exposures may not be causing detectable adverse health effects in most healthy workers."

Response 3: The occupational studies suggest long-term exposure to low levels of perchlorate may not cause adverse effects in healthy adults. However, this conclusion is weakened by the relatively short exposure duration in some cases, intermittent exposure in one occupational study, small number of subjects, and limited number of endpoints investigated. In addition, the OEHHA risk assessment must consider sensitive subpopulations such as pregnant women, their fetuses, and infants.

Comment 4: "OEHHA should establish a single value for its PHG rather than a range of values."

Response 4: OEHHA discussed a range of potential values in the draft PHG document to solicit external inputs on the approaches to characterize the dose-response relationship

and usage of uncertainty factors. In the final document, OEHHA provides a single value of 6 ppb for the perchlorate PHG.

Comment 5: "I do not agree with OEHHA's use of the 0.007 mg/kg-day dose as a NOAEL. One important finding from the Greer *et al.* study is the clear dose-response trend seen in iodine uptake inhibition. I don't believe it can be stated with any certainty that the lower dose in this study represents a NOAEL. At this exposure level for both the 8 and 24-hour uptake measures, iodine uptake on day 14 is lower in the 0.007 mg/kg-day dose group than in the control group. This is true when looking at the raw percentages as well as the percent of baseline. Granted, these differences are not statistically significant. However, given the obvious dose-response trend seen overall, this lack of statistical significance in the lowest exposure group is very likely a matter of inadequate sample size and statistical power."

Response 5: The dose received by the highest dose group whose average response is not statistically different from that of the control group is the conventional way of defining a NOAEL. Using this approach, the NOAEL of the inhibition of NIS data set reported by Greer *et al.* (2002) is 0.007 mg/kg-day. There are inherent limitations in this approach. The NOAEL identified is affected by, among other things, the spacing of the doses selected and the number of subjects in each dose group. For this reason, OEHHA has now used a benchmark dose analysis to more accurately define a no-effect level.

Comment 6: *The reviewer felt OEHHA's presentation of a variety of approaches is very appropriate, and a failure to discuss and compare alternative methods would result in an incomplete assessment. Given the Greer et al. data set and the limitations of the NOAEL approach, the reviewer suggested that the benchmark dose approach is the more valid method and the NOAEL approach should be presented in the context that it is for comparison purposes only.*

Response 6: OEHHA agrees with the reviewer, and has revised the document accordingly.

Comment 7: "Regarding the specifics of the benchmark dose approach as used by OEHHA, I agree with the level of five percent inhibition as the BMD given the level of responses seen in the Greer *et al.* study. I also believe it is appropriate to use the 95% lower confidence interval of the BMD as the BMDL given the precedent for its use in many other risk analyses. The Hill model appears to fit the Greer *et al.* data well, although I would suggest a little more discussion on its selection and would consider presenting a comparison of this model with other models."

Response 7: OEHHA now uses the BMDL for the development of the PHG. OEHHA examined several curve-fitting models provided in the U.S. EPA Benchmark Dose software with the Greer *et al.* data set. The Hill model appeared to be the most appropriate model in terms of both curve-fitting and biological plausibility. However, a more detailed comparison of various model outputs would complicate the discussion without affecting the overall result, so we have decided not to expand this section.

Comment 8: "The health-protective water concentrations for infants would be 0.74 ppb if the uncertainty factor for inter-individual variation were not decreased in this calculation. The explanation for lowering the uncertainty factor for inter-individual variation in the calculations for infants does not seem to be adequately justified. This may give some readers the perception that this factor was lowered simply to make the health-protective water concentration for infants consistent with that for pregnant women and lactating mothers. It may be that by using the BW/WC of infants, some of the uncertainty relating to intra-individual variation has been removed. But, how much?"

Response 8: The footnote of Table 29 of the draft perchlorate PHG stated, "an overall uncertainty factor of 10 is used for infants. It includes an uncertainty factor of 3 for inter-individual variability, and 3 for limitation of the database." In the final PHG, the uncertainty factor of three for interindividual variability for infants is retained at three, and an infant specific body weight/fluid consumption rate ratio is used to estimate the health-protective drinking water level. The infant fluid consumption value accounts for a six times higher exposure rate than that of pregnant women. The database limitation factor is removed (see comments #11 and 12), and the RSC for infants is assumed to be 1.0 (100 percent) to allow for infants whose total diet is formula prepared with perchlorate-containing water. With these changes, the health-protective level for infants is slightly higher than that for pregnant women; this has been clarified in the final PHG document.

Comment 9: *The reviewer concluded that reasonably good arguments could be made for using the BW/WC ratio for pregnant women, lactating women, or infants in determining the final PHG. The reviewer recommended OEHHA use the value for infants (5.99 kg-day/L) since this is a more reasonable, health-protective number.*

Response 9: Using PBPK modeling, U.S. EPA concluded that the human exposure equivalent of a 15 kg child is about the same as a 70 kg adult. In addition, Clewell *et al*. (2003) using PBPK modeling predicted that neonatal rat gets 6-7 fold higher perchlorate dose, on a body weight basis, through the milk pathway than the lactating rat. However, in terms of perchlorate concentration in serum, the value predicted for the neonate is less than that of the lactating rat, which presumably rates to a higher excretion rate in the neonate.

In the final PHG document, an exposure scenario for pregnant women was used in the development of a health-protective drinking water level for perchlorate. For comparison, health-protective drinking water levels were also calculated for lactating women, infants, and adults. All of the values fall within a range of 6-8 ppb.

Comment 10: "Regardless of which value is used for BW/WC however, I would recommend the uncertainty factor for inter-individual variation remain at 10 unless further justification is provided for using a different number based on established policy or scientific validity."

Response 10: A factor of 10 for interindividual variation has traditionally been used in drinking water risk assessment, which would include the variation in dose due to higher exposure levels for children, based on their higher relative water consumption. However, when the calculations provide an explicit adjustment for infants based on their higher exposure, the remaining 'toxicodynamic' uncertainty would correspond to a significantly lower value. In our final calculations, the infant exposure correction amounts to a factor of about six, compared to pregnant females, based on OEHHA water consumption estimates (OEHHA, 2000). We have allocated a factor of three for the remaining interindividual toxicodynamic factors. This is consistent with the PBPK work published by Clewell *et al.* (2003), in which they estimated that the perchlorate dose of the neonatal rat (as estimated by area under the curve of serum perchlorate concentration) is lower than that of the lactating dam or the pregnant female. An interindividual uncertainty factor of 10 is retained in the pregnant woman exposure estimation.

Comment 11: "The Greer *et al.* study involved healthy adults and therefore the results of this study may not represent the effects that may occur in susceptible subgroups. For this reason, I agree with OEHHA's application of an uncertainty factor of 10 for inter-individual variability. I do not however, see adequate justification for the additional uncertainty factor of 3 for database limitations."

Response 11: An overall uncertainty factor of 10 is used for pregnant women and three for infants in the final PHG. Accepting the latter point, no uncertainty factor for database limitation is used in the final perchlorate PHG document.

Comment 12: *The reviewer was not convinced that an uncertainty factor is needed to account for the limited data on immunotoxicity. Furthermore, the reviewer suggested that there is no need for an uncertainty factor to account for the short exposure duration of the Greer et al. (2002) study, if NIS inhibition is chosen as the endpoint.* "There is some evidence in Greer *et al.* that iodine inhibition from short-term exposures is similar to that of longer-term exposures. This is, at all dose levels, inhibition on day 2 was similar to inhibition of day 14. This suggests that iodine uptake is inhibited very quickly after exposure begins and inhibition does not worsen as exposure continue."

The reviewer also stated, "if we can prevent the precursor event, iodine uptake inhibition, then we can prevent the subsequent health effects. Importantly, we do have data from occupational cohorts who have been exposed for many years. Although these studies involve healthy adult workers and not susceptible subgroups, they provide at least some evidence that long-term cumulative exposures do not lead to tremendously high risks of thyroid-associated disease."

Response 12: We agree with these comments, and have decided that the uncertainty factor of three to account for database limitation used in the review draft will no longer be used in the final PHG calculation.

Comment 13: "There was some mention in the public comments about applying an additional uncertainty or safety factor of 10 given the potential neurological effects in

children and the tremendous impact these types of effects could have on children and society as a whole. I agree that the effects of hypothyroidism on fetal and infant development are extremely important and well documented. However, I believe this additional factor is probably not needed. By using the Greer *et al.* results, the calculation of the PHG in the OEHHA document is based on an effect that is not a direct adverse health event, but rather a precursor to an adverse health event. Based on the literature I have reviewed, it appears that there may be a substantial gap between the lowest level of perchlorate that inhibits iodine uptake and the level that will lead to hypothyroidism. Granted, this gap may be larger in some people than others, this is why the uncertainty factor of 10 has been applied for inter-individual variation. Regardless, whatever gap does exist between inhibition of iodine uptake and the development of disease offers at least some additional conservatism in the PHG calculations by OEHHA. Others areas of conservatism in the OEHHA PHG are the use of the 95% BMDL, the use of the BMD05 rather than a BMD10 or a standard deviation approach, the use of the 95th percentile for the WC/BW in susceptible populations, and the rounding down of the final health protective water concentration number."

Response 13: OEHHA agrees with the reviewer, and no additional uncertainty factor is applied in the calculation of the PHG.

Comment 14: *The reviewer felt there is adequate justification for a PHG of 2 ppb. As presented in the OEHHA draft document, a dose-response analysis based on the Greer et al. data can be used to estimate a BMDL of 0.0037 mg/kg-day. Using an uncertainty factor (UF) of 10 for interindividual variation and the BW/WC of 5.99 kg-day/L for infants would yield a PHG of 2 ppb.*

Response 14: A factor of 10 for interindividual variation has traditionally been used in drinking water risk assessment, which would include the variation in dose due to higher exposure levels for children, based on their higher relative water consumption. However, when the calculations provide an explicit adjustment for infants based on their higher exposure, the remaining 'toxicodynamic' uncertainty should correspond to a significantly lower value. In our final calculations, the infant exposure correction amounts to a factor of about six, compared to pregnant females, and we have allocated a factor of three for the remaining toxicodynamic factors.

Comment 15: "Given the logical connection between perchlorate, diminished iodine uptake, hypothyroidism, and thyroid-related health effects, it also seems reasonable to assume that people who are iodine deficient or clinically or subclinically hypothyroid may be more susceptible to the effects of perchlorate than people who are healthy. For this reason, I agree with OEHHA's interpretation of the current literature in defining susceptible subpopulations."

Response 15: No change required.

Comment 16*: The reviewer disagreed with some public comments on the draft perchlorate PHG that, based on the NHANES III data, every person in this country has*

an adequate iodine intake. The reviewer believes that it is more likely that at least some fraction of our population is iodine deficient, and this fraction probably lies somewhere between 0 and 11.7 percent. At least one of the public comments suggested that iodine deficiency is not seen in pregnant women in this country due to the widespread use of prenatal nutritional supplements. The reviewer agreed that the percentage of pregnant women in this country on prenatal vitamins is probably very high, but there is no convincing data showing that it is 100%.

Response 16: We agree; no change required.

Comment 17: "It has also been reported using NHANES III data that 4.3 percent of the US population may be subclinically hypothyroid (24). While the majority of these cases may not be due to iodine deficiency, these data provide additional evidence that a large population of potentially susceptible people could exist in this country."

Response 17: No change required.

Comment 18: "According to the draft document, OEHHA must consider the existence of groups in the population that are more susceptible to adverse effects of contaminants than a normal healthy adult. In my opinion, the dramatic decrease in iodine excretion over the last two decades and the large fraction of subjects identified in NHANES who have subclinical hypothyroidism raises concern that the number of people that may be susceptible to the inhibitory effects of perchlorate on iodine uptake is not trivial."

Response 17: We agree; no change required.

University of California peer reviewer #3

Comment 1: "The section on carcinogenicity does not provide any convincing data that perchlorate is a carcinogen. Follicular cell hyperplasia is a consequence of a TSH-stimulated thyroid gland secondary to iodine deficiency. Thyroid gland enlargement, including benign adenomas, is a consequence of TSH stimulation secondary to hypothyroidism induced by chronic perchlorate treatment in animals. Benign adenomas are not precursors to carcinomas. In essence, no data are presented that show perchlorate, by itself, is a carcinogen."

Response 1: The perchlorate risk assessment has been modified to suggest that perchlorate is a "potential" animal carcinogen, based on the available animal toxicity data and structure-activity relationships. However, because of the mechanistic considerations, OEHHA and the U.S. EPA agree that the risk assessment should not be based on carcinogenicity.

Comment 2: "The study of Crump *et al.* (2000) showed that there was no alteration of thyroid function or incidence of congenital hypothyroidism in Taltal, Chile where the tap water contained 100-120 ppb perchlorate compared with two other regions of Chile with

low or no perchlorate in the water. The draft omits the data of Table 2 in the paper which reported that urine iodine is 947 mcg/g creatinine in Taltal and similar in the comparison areas. These urine iodine data indicate that iodine intake was very high, about 5-fold increased compared with urine iodine in the United States. Such a high iodine intake would overcome the potential effect of perchlorate on inhibition of thyroid function."

Response 2: Urine iodine levels reported in the Chile study have been added to the document.

Comment 3: "The study of Greer (2002) showed that the results with two days of perchlorate were similar to those with 14 days of perchlorate treatment. Presumably a longer duration of perchlorate ingestion would not result in a greater effect in regard to inhibition of thyroid uptake. This work and a similar study showed no effect of perchlorate on serum TSH or T4, but the duration of these studies is insufficient to deplete the thyroid gland's store of thyroid hormone in euthyroid individuals."

Response 3: We agree. In the risk assessment, OEHHA does not apply an uncertainty factor to account for the short exposure duration. OEHHA also agrees with the reviewer that the information about serum TSH and T4 in the Greer *et al.* (2002) study is not as useful as the NIS inhibition data.

Comment 4: "The draft contains an excellent summary of the literature on thyroid function in pregnancy, pointing out the dangers of low iodine intake in pregnancy that could result in maternal goiter and hypothyroxinemia. There are appropriate summaries of the relevant rat data from the Escobar group. However, the excellent studies of Hetzel on low iodine intake in pregnant sheep resulting in altered brain morphology of the fetus and newborn are not described."

Response 4: The studies of Hetzel on low iodine intake in pregnant sheep have been added to the document.

Comment 5: "The review of human data showing that maternal hypothyroidism can result in reduced thyroid function is appropriate. The data of Haddow (1999) are especially important. The work of Pop *et al.* (1999) has recently been extended in a new study showing that children of women who had low free T4 at 12 and 24 weeks gestation had developmental delay at 2 years of age (Clinical Endocrinology (2003; **59:**282–288)."

Response 5: The recent work of Pop *et al.* has been added to the document.

Comment 6: "A study of deceased preterm and term infants showed that their thyroid glands have only small stores of thyroxine in thyroglobulin, the storage protein in the colloid of the thyroid gland (van den Hove MF, Beckers C, *et al.* Biochimie 1999; 81:563-70). These investigators estimated that the turnover of the thyroxine pool of these thyroids is 100%/day. Because of high turnover within the fetal preterm and term thyroid, iodide depletion could lead to deficient hormone secretion very readily compared

with the adult. (Note that the adult human thyroid in regions of iodine sufficiency has a two to three month reservoir of thyroid hormone.) Depletion of fetal thyroxine could result in deficient neurological and cognitive development."

Response 6: The study mentioned in this comment has been added. OEHHA agrees with the reviewer that the fetus is one of the sensitive populations to be protected by the PHG, for the reasons cited.

Comment 7: "In regard to the calculation of the PHG, I agree with the use of BMDL. The relative source contribution (RSC) of 80% allows for 20% intake of perchlorate through possible foodstuffs which seems to provide another safety factor that is reasonable. The body weight/water consumption (BW/WC) of 25.2 kg/day/L for ratio of body weight and water consumption is at the 95th percentile, and thus again provides a safety margin."

Response 7: OEHHA has continued to use the BMDL for calculation of the PHG. Due to the availability of additional produce sampling data, OEHHA lowered the RSC to 60 percent in the final perchlorate PHG document.

Comment 8: "The rationale for the uncertainty factor (UF) of 30 is not effectively justified. I think it is more reasonable to use a factor of 4 for inter-individual variability in a human database. Since data are available for this calculation, I see no rationale for adding another factor of 3 for limitations of the database. Therefore, I recommend using a UF of 4. The PHG calculation then becomes 3.7 kg-day x 0.8 x 25.2 kg-day/L x 1/4. **This leads to a concentration of 18.6 mcg/L as the PHG."**

Response 8: In view of the relatively small number of subjects in the Greer *et al.* (2002) study, the iodine-replete status of the subjects, and the lack of individuals in the study who are potentially sensitive to the anti-thyroid effects of perchlorate, OEHHA believes that a substantial allowance for interindividual variability must be incorporated. The reviewer bases the factor of 4 on the iodine excretion rates of pregnant women, whereas there are several other considerations. Among these are the extra need for thyroid hormone during pregnancy, and the exposure and thyroid status of the fetus. Using PBPK modeling on rat data, Clewell *et al.* (2003) show the possibility of a greater effect of perchlorate in the fetus than in the mother, which may be related to direct effects of perchlorate on the fetal thyroid and a reduction of iodine transport across the placenta. Furthermore, fetal development is also affected by changes in maternal thyroid hormone levels. For these reasons we have retained the use of a default factor of 10 for pregnant women.

Comment 9: "I believe that the fetus represents the most vulnerable segment of the population. This implies that pregnant women are the target population for the PHG. The basis for this conclusion is that hypothyroidism in the mother may result in reduced cognitive function of the child. Therefore, maternal hypothyroidism and low iodine intake must be avoided."

Response 9: OEHHA agrees with the reviewer in identifying the pregnant woman with marginal iodine deficiency and her fetus as sensitive populations, but also includes calculations for lactating women and infants.

Comment 10: "In theory, patients with compromised thyroid function, such as those with untreated subclinical hypothyroidism, may be affected more readily by significant perchlorate ingestion. This size of this group increases with aging and becomes 5 to 15% of the elderly population. Exacerbation of the thyroid condition could lead to adverse consequences, such as the development of overt hypothyroidism with increased cardiac morbidity and mortality. However, worsening hypothyroidism in this group could be detected by screening and corrected with thyroxine therapy, thus avoiding the consequences. The adverse effects of hypothyroidism occur slowly in adults and can be corrected completely. Therefore, I consider that the consequences of perchlorate exposure in this population are not as severe as those in the fetus."

Response 10: OEHHA agrees with the reviewer.

Comment 11: "The uncertainty factor consists of two components. First, a component of 10 for inter-individual variability. The principal rationale for this, as I see it, is that pregnant women were not studied in the benchmark study of Greer (2002). Pregnant women have increased renal iodide excretion so they are more vulnerable. This vulnerability is far less than would be accounted for by a factor of 2. Including another factor of 2 provides an additional safety margin. Therefore, a UF of 4 seems reasonable."

Response 11: OEHHA believes that a UF of 4 understates the total uncertainty because it is based, according to the reviewer's statement, solely on pharmacokinetic variability. We agree with the comment that the vulnerability of pregnant women related to increased iodide excretion should result in less than a factor of 2 difference, but we also consider additional requirements for thyroid hormone output in pregnancy, and direct effects of perchlorate on the growing fetus.

Comment 12: "The second component of UF accounts for limitations of the database. Although ideal studies have not been performed yet and additional studies are highly desirable, especially long-term human studies, there are data in prospective short-term human and longer-term animal studies that are not widely discrepant. The retrospective epidemiologic data are discrepant, but do not clearly show significant consequences of perchlorate exposure. Because of these reliable, short-term human and animal prospective studies, I do not believe that an additional uncertainty factor of 3 is justified."

Response 12: An uncertainty factor of three for the limitation of the database is no longer used in the risk assessment.

Comments from Larry Ladd, Rancho Cordova community representative

Comment 1: "One of the strengths of this particular draft is that it is relatively simple for the public to understand and support: Only 5% blockage of NIS iodide uptake is tolerated, with the addition of an uncertainty factor of 10 for sensitive individuals and an additional uncertainty factor of 3 to cover the potential for other unknown toxic mechanisms."

Response 1: OEHHA appreciates the favorable comment. It should be noted that in the final risk assessment, the overall uncertainty factor has been reduced from 30 to 10. Reviewers of the second University of California peer review recommended OEHHA should not apply an uncertainty factor for the short exposure duration in the Greer *et al.* (2002) study and the limitation of the database, and we concur with this advice.

Comment 2: *The benchmark dose software seems to be such a critical component of the analysis, further explanation of its merits should be included in the document.*

Response 2: OEHHA has added some background information on the benchmark dose software and sources of reference material provided by its developer, the U.S. EPA.

Comment 3: *There appeared to be a difference in the interpretation of the immunotoxic studies (Burleson et al., 2000) by OEHHA and U.S. EPA. "On page 30 OEHHA states: 'Exposure to a lower dose of 2 mg/kg-day did not affect the response in both the 14-day and 90-day studies,' while page 5-102 of the US EPA document reads 'The results of the effect that 14- and 90-day exposure to ammonium perchlorate has on the development of contact hypersensitivity response to DNCB, as determined by LLNA, indicate that ammonium perchlorate dose as low as 0.06 mg/kg-day enhances this response.'*

Response 3: The apparent difference in interpreting the immunotoxicity data has been fixed. The discussion of the test results has been reworded. Although U.S. EPA stated on pages 5-101 and 5-102 of their risk assessment document (U.S. EPA, 2002) that ammonium perchlorate doses as low as 0.06 and 0.2 mg/kg-day increased contact hypersensitivity response to 2, 4-dinitrochlorobenzene (DNCB), as determined by local lymph node assay (LLNA), it also pointed out that no increase in response was noted at a higher dose of 2 mg/kg-day. The interpretation of these results was further complicated by the fact that cyclophosphamide, a positive control, suppressed response of the test system in the 14-day, but not in the 90-day studies.

Comment 4: "On pages 37-38 there is a discussion of Crump's study of Chilean school children. OEHHA states, 'It must be emphasized that in addition to perchlorate exposure, a low dietary iodine uptake might have also contributed to increased thyroid problems reported in the residents of Taltal.' If my recollection of Dr. Crump's August 2000 presentation in San Antonio is correct, Taltal is a fishing village. So if anything, a traditionally high dietary iodine uptake in Taltal may have increased thyroid problems, at least in terms of autoimmunity."

Response 4: An increase in thyroid problems mentioned in the comment probably refers to the increased historical thyroid diseases experienced by the family members of the school children surveyed. A portion of the disease could have happened decades ago, before the introduction of iodized salt in 1982.

Judging by the urinary iodine levels in schoolchildren, there appears to be no iodine deficiency in the three cities studied by Crump *et al.* (2000). The mean urine iodine levels reported for Antofagasta [75.6 µg/dL], Chañaral [61.4 µg/dL], and Taltal [76.6 µg/dL] are higher than those measured in the U.S. However, the report also found high prevalence rates of goiter among school-age children in the three cities (Chañaral [26.5 percent], Taltal [23.3 percent], and Antofagasta [17 percent]). If the urinary iodine data are accurate, there are some other factors that are contributing to the high goiter rate in the children.

Comments from Thomas Zoeller, University of Massachusetts, Amherst

Comment 1: "Unlike normal euthyroid adults such as those included in the study by Greer *et al.* [1], late gestation fetuses and early neonates have no capacity to store thyroid hormone in their thyroid glands. In fact, van den Hove *et al.* [2] recently published an empirical study concluding that the amount of thyroid hormone contained in a neonate's thyroid gland is insufficient to supply the child with thyroid hormone for a single day. Thus, thyroid hormone synthesis in the neonatal thyroid gland must occur daily to maintain circulating levels of thyroid hormone. This observation is important because it illustrates very clearly, and with a solid basis in the literature, that the fetus and neonate are quite different from adults. … The report by van den Hove is a clear and important demonstration of the differences between adults and infants."

Response 1: The data reported by van den Hove *et al.* (1999) have been added to the risk assessment. The study result supports the use of an uncertainty factor to account for differences in interindividual susceptibility to the effects of perchlorate.

Comment 2: *Another important difference between adults and the fetus/neonate is the relative degree to which they can sustain thyroid hormone insufficiency without permanent damage. There are uncertainties in the relationship between an insufficient iodide uptake and a decline in the circulating levels of thyroid hormones as well as the relationship between a decline in the circulating levels of thyroid hormones and adverse neurological deficits in neonates. However, we do know that subtle differences in the dose of thyroid hormone given to children with congenital hypothyroidism are associated with differences in a number of neurological parameters (Heyerdahl, 2001; Heyerdahl et al., 1991; Rovet et al., 1987; Rovet, 2000; Song and Rovet, 2001). In addition, the duration between birth and the onset of T4 treatment in children diagnosed with congenital hypothyroidism is an important variable impacting neurological development, and some authors indicate that as little as 14 days of exposure to thyroid hormone insufficiency can produce measurable neurological deficits (van Vliet, 1999).*

Response 2: Some of the key studies suggested by the commenter have been added to the risk assessment. The fact that neonates have less thyroid hormone stored in the thyroid gland, subtle decreases in circulating thyroid hormone may permanently impact brain

development, and the duration of exposure to this insult required for damage to occur appears to be relatively short, are reasons supporting the identification of infants as one of the sensitive subpopulations. It is important to realize that when NIS inhibition is avoided, there should be no reduction in iodide stored in the thyroid and consequently no impairment of thyroid function.

Comment 3: "[W]e know that perchlorate will inhibit iodide uptake into the milk [9-16], and that perchlorate likely is preferentially taken up into milk [10]. This is true both for the human and for dairy animals that contribute products for human consumption. Specifically, to what extent does perchlorate make it into infant formula, either from tap water itself, or from dairy products? Does perchlorate and genestein (a TPO inhibitor, [17]) in soy formula interact to reduce thyroid function? How comfortable are we that the fetal/neonatal thyroid gland is in fact no more sensitive to perchlorate than the healthy adult volunteers of the Greer study?"

Response 3: At high doses, perchlorate inhibits the secretion of iodide into the milk, as confirmed in a number of species. If one assumes the behavior of NIS in the mammary gland is similar to that of the NIS in the thyroid, there should be no reduction in iodide in breast milk when the nursing mother is exposed to perchlorate in drinking water at the PHG level. Recently, perchlorate has been detected in cow's milk (1.7-6.4 µg/L), evaporated milk (1.1 µg/L), and human breast milk (4 µg/L) (Kirk *et al.*, 2003). The authors could not detect perchlorate in a reconstituted powdered milk sample. While the number of samples is very small (one breast milk sample and one evaporated milk sample), the results do not indicate a large concentration factor for perchlorate in milk.

It is possible that a NIS inhibitor and a TPO inhibitor could act synergistically but we have no data to confirm that. OEHHA is not aware of any specific data regarding co-exposure to perchlorate and genistein.

Using PBPK modeling on rat data, Clewell *et al.* (2003) show the possibility of a greater effect of perchlorate in the fetus than in the mother, which may be related to direct effects of perchlorate on the fetal thyroid and a reduction of iodine transport across the placenta. Furthermore, fetal development is affected by changes in maternal thyroid hormone levels. For these reasons we have retained the use of a default factor of 10 for the risk assessment for pregnant women.

Comments from Gina M. Solomon, Natural Resources Defense Council

Comment 1: *The commenter suggested that the study by Greer et al. is not suitable for setting the PHG because it has serious scientific and ethical weaknesses. Also, it is said that* "EPA's Science Advisory Board and Scientific Advisory Panel have jointly recommended against considering such human studies to establish NOAELs or NOELs for pesticides, based upon scientific and ethical grounds that apply equally to such tests of other industrial chemicals such as perchlorate." *Also* "There is a rich database of animal toxicology studies upon which we suggest that OEHHA should base a PHG."

Response 1: The work reported by Greer *et al.* (2002) was supported by the Perchlorate Study Group and by a National Institute of Health grant and appears to conform to standard practices for human studies. All volunteers were asked to sign an informed consent form which was approved by an Institutional Review Board (IRB). The use of human data and the identification of the Greer *et al.* (2002) study as the critical study for quantitative human risk assessment have been supported by the second University of California peer review (OEHHA, 2004). Recently, the National Academy of Sciences completed its review of the use of human data for establishing NOAELs for pesticides and concluded that human studies could be justified.

Comment 2: "Even if we assumed that the Greer study was ethically and scientifically justifiable (which we certainly do not), OEHHA must review all consent and volunteer information forms and the underlying paperwork, data, and information to confirm the voluntariness of consent, and compliance with all requirements of these codes and rules, such as conflict of interest and disclosure requirements."

Response 2: OEHHA does not carry out the kind of in-depth investigation of the underlying procedural paperwork of a peer-reviewed study suggested by the commenter. The Greer *et al.* (2002) study was conducted by an established and reputable scientific investigator, was published in a reputable scientific journal, Environmental Health Perspectives, and the study data are consistent with the current toxicity data on perchlorate.

Comment 3: *The commenter criticized the study by Greer et al. for its small sample size, for not including susceptible subgroups of concern (i.e., pregnant women and infants), and for having subjects that had normal thyroid function and were nutritionally replete with iodine. The commenter also criticized the short exposure duration of the study saying that effects that are likely to appear over time as endogenous thyroid reservoirs fall, would not show up in the study. Also, the Greer et al. study focused on the effects of perchlorate on thyroid functions, and could have missed other low-dose effects. Although OEHHA added uncertainty factors to address some of the concerns, it is unlikely that the chosen uncertainty factor is sufficient to address all the weaknesses of this study.*

Response 3: OEHHA agrees with the commenter that there are limitations in the human data reported by Greer *et al.* (2002). In OEHHA's final risk assessment, an uncertainty factor of 10 is used to extrapolate the results from the study results to the general population, including sensitive subgroups. The Greer *et al.* study focused on the inhibition of NIS because, based on the available toxicological information, this is the first step in the thyroid hormone perturbation and this is likely to be the most sensitive endpoint. It is possible that there are other biological and health effects related to perchlorate exposure at low doses; however, no specific information is available at this time.

The reviewers of the second University of California peer review (OEHHA, 2004) support OEHHA in the use of human data and the identification of the thyroidal iodide uptake data reported by Greer *et al.* (2002) as the critical study for dose-response

characterization. The reviewers also recommended that OEHHA not apply an uncertainty factor for the short exposure duration of the Greer *et al.* study and database limitations.

Comment 4: *The commenter does not agree with an OEHHA statement: "Rodents are found to be more susceptible than humans to the perturbation of thyroid hormone homeostasis by perchlorate." The commenter said OEHHA contrasts rodent studies done with adequate sample size and statistical power in a susceptible population (fetuses), with human studies that contain the numerous methodological weaknesses enumerated above. The Greer et al. data simply demonstrate a scientific truism: that poor study design can fail to show health effects even where they do exist.*

Response 4: The statement objected to by the commenter is not based on animal developmental studies and the Greer *et al.* study alone. Short-term rat studies of Caldwell *et al.* (1995) and Springborn (1998), for example, show effects on the thyroid-pituitary axis at perchlorate doses lower than those causing similar effects in humans. Humans have thyroxine-binding globulin in the blood that binds thyroxine (T4) and increases the biological half-life of T4 (5-9 days), while rats do not have this protein and the half-life of their T4 is only 0.5-1 day. Because of this difference, thyroid of rats is under constant stress and its T4 production rate per body weight is about 10 times higher than that of humans. The several reasons why OEHHA believes rodents are more sensitive to thyroid hormone perturbation have been discussed at greater length in the risk assessment.

However, we have clarified in the final document that the comparison is to healthy adults in a short-term study. We do not have adequate information to compare rodents to the sensitive subpopulations.

The reviewers of the second University of California peer review (OEHHA, 2004) support OEHHA in the use of human data and the identification of the thyroidal iodide uptake data reported by Greer *et al.* (2002) as the critical study for dose-response characterization.

Comment 5: *The commenter does not believe the uncertainty factors used in the draft are sufficient to cover all the uncertainties in extrapolating from the Greer et al. data to the general population as well as the existing data gaps.*

Response 5: As discussed above in relation to their comments, the reviewers of the second University of California peer review (OEHHA, 2004) support OEHHA in the general approach of the perchlorate risk assessment and the selection of the critical study for dose-response characterization. The reviewers also recommended that OEHHA not apply an uncertainty factor of three to account for the short exposure duration in the Greer *et al.* study and the limitations of the database. They also believe it is not necessary to apply an additional uncertainty factor for the data gaps in the immunotoxic effects of perchlorate.

Comment 6: *OEHHA enumerates factors that could result in interactive or synergistic effects, including vegetarian diet, other environmental contaminants, and tobacco smoke. Yet OEHHA fails to consider these factors in setting the PHG. In many areas, Californians are drinking water laced with a mixture of perchlorate and nitrate. It is clear that nitrate can act additively or synergistically with perchlorate. OEHHA is required to take this information into account when setting the PHG and must do this in a quantitative fashion by including an uncertainty factor to account for this identified problem.*

Response 6: Due to the lack of data on relative potencies and exposure levels, quantitative evaluation of the potential interactive effects of many environmental goitrogens and perchlorate exposure is not possible at this time. OEHHA applied an uncertainty factor of 10 to a sensitive endpoint, inhibition of NIS, in the development of the PHG. In addition, OEHHA used a number of health-protective assumptions in the exposure assessment.

In a human study reported by Lambers *et al.* (2000), ten volunteers on an iodine-restricted and low-nitrate diet were exposed to 11 mg nitrate/kg-day (approximately 770 mg/day) for 28 days and did not experience any thyroidal iodide uptake inhibition. The nitrate dose used was three times the allowable daily intake of the study country, Netherlands. On the other hand, van Maanen *et al.* (1994) reported that consumption of water with high nitrate levels (nitrate via drinking water = 109.5 mg/24 hr) was correlated with thyroid enlargement, compared to a control group. The average iodine intake level of subjects ranged from 165 – 179 µg/24 hr. The study was limited by having only 10 subjects in the group exposed to high nitrate levels and some of the confounders were not controlled. These data suggest nitrate in drinking water at levels exceeding 50 mg/L is associated with hypertrophy of the thyroid. OEHHA interprets these somewhat contradictory results as supporting a need for caution.

Comment 7: *The commenter cited the possible bioaccumulation of perchlorate in lettuce and breast milk. It was suggested that the relative source contribution of 80 percent assumed in the second public review draft is too high.*

Response 7: Recently, perchlorate has been detected in cow's milk (1.7-6.4 µg/L), evaporated milk (1.1 µg/L), and human breast milk (4 µg/L) (Kirk *et al.*, 2003). Kirk *et al.* did not detect perchlorate in a reconstituted powdered milk sample. While the number of samples is very small (one breast milk sample and one evaporated milk sample), they do not indicate a large concentration factor for perchlorate in milk. Similarly, several research groups reported the detection of perchlorate in lettuce, cucumbers, strawberries, grass, and other plants. In light of these new data, the relative source contribution in the final risk assessment has been lowered to 60 percent.

Comment 8: *The commenter criticized OEHHA for not identifying infants as a sensitive subpopulation in the summary, stating,* "Neonates and infants must be included as a susceptible subpopulation due to increased susceptibility to irreversible neurological effects from perchlorate-associated iodine deficiency in the central nervous system, as

well as due to increased exposure due to a greater relative consumption of fluids as a proportion of body weight. Breastfeeding neonates and infants must also be considered susceptible due to the evidence that perchlorate is actively sequestered in breast milk."

Response 8: Infants and neonates are identified as one of the sensitive subpopulations in the final risk assessment. Infants and neonates are more susceptible to the effects of iodine deficiency because of the growing central nervous system and because the storage of T4 in the thyroid is relatively small compared to the rate of turnover.

The serum concentration of perchlorate of a neonate may not be higher than that of the nursing mother. In the PBPK work published by Clewell *et al.* (2003), they estimated that the serum perchlorate dose of the neonate rat is lower than that of the lactating rat as well as the pregnant rat. In terms of inhibition of thyroid iodide uptake, Clewell *et al.* (2003) predicted that the fetal rat is the most sensitive subgroup at low doses (0.01 –0.1 mg/kg-day), compared with the male rat, the pregnant rat and the lactating rat. While the absorption, distribution, and excretion of perchlorate in humans may not be strictly comparable to the rat, this modeling work does indicate that the effective systemic dose received by an infant via breast milk may not be as high as suggested by the infant's fluid consumption rate/body weight ratio.

Comment 9: *The commenter questioned why OEHHA assumed an uncertainty factor of 30 for pregnant women and only an uncertainty factor of 10 for infants in the second public review draft.*

Response 9: Generally, the default assumption is to use an uncertainty factor of 10 for interindividual variability. Of that factor of 10, 3 (or half a log unit) is assumed to account for differences in toxicokinetics and another 3 is for differences in toxicodynamics. In estimating a health-protective water concentration for infants, the toxicokinetic difference between the study population and infants is already considered by using the infant's fluid consumption and body weight ratio in the estimation. A factor of three was then applied for possible variations in toxicodynamics.

In the review draft, an uncertainty factor of three was used to account for database limitations in estimating perchlorate dose for both infants and pregnant women. In the final PHG document, OEHHA takes the recommendations of the second and third University of California peer reviewers (OEHHA, 2004) and no longer applies this uncertainty factor in the human health risk assessment.

Comment 10: *The commenter acknowledged some of the advantages of using the benchmark dose approach in analyzing dose-response data. The commenter cautioned that it is important to explain the model and the calculation so that it can be understood and replicated by external reviewers. The commenter also cautioned that the selection of the benchmark dose be done in a health-protective manner, and argued that it would not be appropriate to use a benchmark dose of 10 percent or use BMD instead of the more health-protective BMDL.*

Response 10: We agree; no response required.

Comments from Kevin P. Mayer, Region IX, U.S. Environmental Protection Agency

Comment 1: *The commenter disagreed with the decision to increase the relative source contribution from 60 percent to 80 percent in the second public review draft. A relative source contribution of 0.8 conventionally indicates an assumption that water supply is the principal source of exposure. The limited data on plant uptake does not support such an assumption.*

Response 1: OEHHA concurs; based on the recently available produce data, OEHHA uses a relative source contribution of 60 percent (0.6) in the final perchlorate PHG document.

Comments from George W. Rutherford, University of California, San Francisco

Comment 1: *The commenter suggested that serum TSH is considered more reliable, sensitive and less ambiguous as a screening indicator for the evaluation of potential primary congenital hypothyroidism than serum T4. Since December 1997, the California Newborn Screening Program no longer uses a T4 first-stage screening test and instead relies entirely on the measurement of TSH. The commenter believes this should be considered when reviewing the epidemiologic literature on thyroid function and environmental perchlorate exposure.*

Response 1: Noted; the variability in T4 in blood is one reason why we have chosen to use the data on iodide uptake inhibition as the basis for the PHG.

Comment 2: *In their work, the commenter has found that ethnicity, gender, and birth weight were risk factors for primary congenital hypothyroidism, while specimen collection time and year had the most pronounced effect on TSH levels. In addition, risk factors for primary congenital hypothyroidism are not necessarily the same as risk factors for elevated TSH levels.*

Response 2: Noted; no response required.

Comments from Joan S. Dollarhide and Michael L. Dourson, Toxicology Excellence for Risk Assessment

Comment 1: *The commenters suggested that the decrease in serum T4 should be treated as the critical effect of perchlorate exposure. This effect, while not adverse in itself, is a precursor that leads to subsequent adverse effects in thyroid homeostasis and neurological development. They noted that data in humans show that inhibition of iodide uptake up to 70 percent has not resulted in decreased T4 levels, even after long- term exposures (this understanding integrates the results of several human studies). Therefore, designating 5 percent iodine uptake inhibition as an adverse effect is inappropriate*.

Response 1: As noted by the previous commenter, there are problems with interpreting serum T4 data. Conceptually, it is difficult to understand how a 70 percent reduction in thyroidal iodide uptake on a long-term basis would not lead to a decrease in serum T4 or an elevation in serum TSH. There is expected to be a "margin of safety" between the inhibition of thyroidal iodide uptake and other thyroidal effects such as depression of serum T4, elevation of serum TSH, and enlargement of the thyroid gland. However, the margin is likely to vary from person to person depending on a number of factors, including amount of iodide stored in the thyroid, exposure to other environmental goitrogens, pre-existing thyroid illnesses, and pregnancy. This margin of safety is acknowledged but not numerically incorporated into the calculation of the PHG, since the available data are insufficient to delineate the dose-response relationships. This is one of the reasons that OEHHA applies a relatively small overall uncertainty factor of 10 in the final perchlorate risk assessment.

Comment 2: "Since no available human studies have measured a decrease in T4 following perchlorate exposure, another reasonable approach is to use the excellent dose-response data on iodine uptake inhibition from the Greer *et al.* study as a point-of-departure for a perchlorate RfD, recognizing the inherent uncertainty already accounted for in this conservative approach."

Response 2: The approach used in the development of the perchlorate PHG is similar to the one suggested by the commenter. OEHHA selected the human study reported by Greer *et al.* (2002) as the critical study for dose-response evaluation, and used the BMDL to represent the point-of-departure. However, OEHHA also recognizes the differences between the study population and the target population and included an uncertainty factor of 10 to account for interindividual variability.

Comments from John P. Gibbs, Kerr-McGee Shared Services, LLC

Comment 1: *The commenter suggested that there is a contradiction in the draft risk assessment.* "On page 15 of the draft, it said that "It is not clear whether this anion sequence (that shows the relative potency of perchlorate, thiocyanate, and nitrate), measured at very high concentrations, has any necessary mechanistic relation to what occurs in the thyroid at low concentrations." However, on page 80, the draft said that dietary iodine intake and thyroidal function are known to vary among individuals affected by goitrogens in food. Thiocyanate and nitrate are some of the common goitrogens in food."

Response 1: The intent of the information presented in the PHG document is that it is not clear whether the relative potency information for these anions derived from *in vitro* experiments is directly applicable to environmental exposures. OEHHA does not dispute the fact that thiocyanate and nitrate at sufficiently high concentration are goitrogens.

Comment 2: *The commenter stated that* "Perchlorate is 10-20 times more potent than thiocyanate and about 200 times more potent than nitrate in inhibiting iodine uptake," *while noting that both thiocyanate and nitrate are present in our diet and/or environment at levels that are orders of magnitude greater than perchlorate. The commenter also said* "In the following brief analysis, we show that extensive evidence from the peer reviewed published literature indicates that dietary nitrates and thiocyanates as well as environmental nitrate exposures contribute far more to iodine uptake inhibition than perchlorate at environmentally relevant concentrations in California."

Response 2: There is contradictory evidence regarding the relative potency of perchlorate and nitrate. Based on the thyroidal iodide data published by Greer *et al.* (2002) on perchlorate and Lambers *et al.* (2000) on nitrate, it can be estimated that perchlorate may be up to 3,000-fold more potent than nitrate. On the other hand, van Maanen *et al.* (1994) reported that consumption of water with high nitrate levels (nitrate via drinking water = 109.5 mg/24 hr) was correlated with thyroid enlargement, compared to a control group. They suggested that nitrate in drinking water at levels exceeding 50 mg/L is associated with hypertrophy of the thyroid, which would imply a significantly higher potency of nitrate for inhibition of iodide uptake.

OEHHA agrees that dose and potency are equally important in assessing the relative importance of various goitrogens in the diet and in the environment. The awareness of these environmental goitrogens supports the need for a more health-protective level of perchlorate in drinking water, not less.

Comment 3: *The commenter raised the issue that nitrate exposure could be a confounding factor in the study reported by Crump et al. (2000).*

Response 3: Noted.

Comment 4: *The commenter presented some preliminary and unpublished data on the serum and urine levels of perchlorate in school-age children in Antofagasta and Taltal.*

Response 4: Given the nature of the data presented, it is difficult to assess their quality and meaning. Furthermore, only 10 serum and urine sample results of each city were provided. It is not clear if they are representative of the 53 and 60 schoolchildren studied in Antofagasta and Taltal, respectively.

Comment 5: *The commenter suggested OEHHA include studies by Morgan et al. (2002) and Li et al. (2001) in the section on the carcinogenicity of perchlorate.*

Response 5: These two studies are now included in the final risk assessment.

Comment 6: *It is suggested that chemicals such as genistein in soy might have interacted with iodine deficiency and perchlorate, and contributed to the overall unreliability of the rat as a model. It is suggested that because rats are already in a near hypothyroid state due to the soy diet, it is impossible to adequately define the NOAEL/LOAEL boundary of*

perchlorate alone. The commenter also said the draft has not taken the synergistic effect of soy into account in interpreting the findings in the rat studies.

Response 6: The potential effects of soy in the diet used in the rat studies are speculative at this time. OEHHA acknowledges the possibility of an interaction between perchlorate exposure and a diet rich in soy. However, OEHHA notes the consistency of findings in the rat studies and the dose-response relationships observed in many instances. The animal toxicity data were mainly used to understand the mode of action of perchlorate and the many adverse health effects related to thyroid hormone disruption. For quantitative evaluation, OEHHA relies on the thyroidal iodide uptake data reported in the human study of Greer *et al.* (2002).

Comments from Kenny Crump and Gay Goodman, consultants for Kerr-McGee Corporation

Comment 1: *The commenters applied a benchmark dose model to the individual raw inhibition of radioiodine uptake (RAIU) data of the Greer et al. (2002) study and defined the benchmark dose either by the standard deviation method or a hybrid method. Furthermore, they built a model that links RAIU, perchlorate dose and spot iodine excretion. They found that when the model did not include "iodine excretion interaction", the BMDLs ranged from 0.0031 to 0.010 mg/kg-day. When the iodine excretion was set to 300 µg/day, the model that included "iodine excretion interaction" predicted BMDLs ranging from 0.0024 to 0.0081 mg/kg-day; when the iodine excretion was set to 100 µg/day, the model that included "iodine excretion interaction" predicted BMDLs ranging from 0.0074 to 0.024 mg/kg-day.*

The commenters asserted that according to their interaction model, the sensitivity to perchlorate inhibition of RAIU was lower when the iodine excretion was lower. They also found the model with "iodine excretion interaction" described the data much better than the model without the interaction. Based on these reasons, the commenters recommended a BMDL of 0.015, the geometric mean of three BMDLs derived from the model with "iodine excretion interaction" and with iodine excretion set to100 µg/day.

Response 1: The commenters applied benchmark dose methods to a set of RAIU and iodine excretion data that have not been peer reviewed and published. Depending on the assumptions and model parameters used, they produced a range of BMDLs that includes the BMDL (0.0037 mg/kg-day) estimated by OEHHA. The validity of the model that links RAIU, perchlorate dose and spot iodine excretion has not been independently verified, and OEHHA finds it difficult to reproduce and use this approach.

Comment 2: *The commenters compared their modeling methods with OEHHA's approach and stated* "Among other advantages, direct modeling of RAIU values permits separation of inter-individual variability from other sources of variability. Also, OEHHA modeled only the 24-hr RAIU data whereas the present approach incorporates both the 8- and 24-hr data into a common analysis."

Response 2: OEHHA performed the dose-response evaluation based on the information published by Greer *et al.* (2002). While incorporating the 8-hr RAIU data into an analysis might help account for variability in the study data, OEHHA believes that the major source of human variability is among the population at large, including sensitive subgroups. A more intensive analysis of the Greer *et al.* data could have only a minor effect on the risk assessment.

Comment 3: *OEHHA used a 5 percent decrease in mean RAIU for defining the BMD. No basis was given for the assumption that such a decrease is generally considered to be biologically significant, as required by the U.S. EPA (2000) draft Benchmark Technical Guidance Document.*

Response 3: OEHHA takes the position that a BMD of 5 percent is conceptually similar to a no-observed-effect level (NOEL), rather than a lowest-observed-effect level (LOEL). Different uncertainty factors would be appropriate for different effect levels. In this context, OEHHA has chosen uncertainty factors it believes to be appropriate for an endpoint considered comparable to a NOEL.

Comment 4: "The U.S. EPA further recommended that the "BMD corresponding to a change in the mean response equal to one control standard deviation from the control mean should also be presented for comparison purposes.." *Thus a complete application of the U.S. EPA guidelines would have required OEHHA to also calculate the BMD using the alternative method.*

Response 4: The alternative method was not used because there was no control group in the Greer *et al.* study.

Comments from Steven H. Lamm and Offie P. Soldin, Consultants in Epidemiology and Occupational Health, Inc.

Comment 1: "The Draft RA has proposed sensitive sub-populations in California under the false assumption that California has an iodine deficient sub-population."

Response 1: Based on the NHANES III data, the U.S. population is not considered iodine deficient. However, the data also suggest that a small percentage of pregnant women and lactating women may be getting less than the optimal amount of iodine from their diet. NAS (2001) recommends much higher iodine intakes for pregnant women and lactating women than that for the general population.

Comment 2: "The fetus is not a sensitive population with respect to perchlorate exposure because of the protection of being inside the mother. Thyroidal maintenance of the embryo-fetus is provided by the maternal thyroid. The best scientific information indicates that the fetus is not dependent upon its own thyroid for thyroidal function."

Response 2: During early pregnancy, thyroid hormone needs of the fetus are satisfied by the transfer of maternal T4. Later, the needs are satisfied by both the maternal T4 and the

T4 produced by the fetal thyroid. The PBPK work published by Clewell *et al.* (2003) predicted that in terms of thyroidal iodide uptake inhibition by perchlorate, the rat fetus is more sensitive than the pregnant rat, the male rat, and the neonatal rat.

Comment 3: *The commenters cited a study showing neonatal thyroxine levels taken just after birth are no different for those children subsequently diagnosed with ADHD or with autism or other neurobehavioral diseases of childhood. They also suggested that ADHD and autism prevalences in Clark County, where there are significant levels of perchlorate in drinking water, are not higher than for Washoe County or the rest of the state of Nevada. Furthermore, several studies show no decrease of neonatal thyroxine levels in areas with perchlorate exposure. Thus, they disagreed with the draft risk assessment suggestion that perchlorate exposure might lead to fetal hypothyroidism and neurobehavioral disorder in children.*

Response 3: OEHHA has taken no position as to whether neurological effects could or should be detectable at drinking water levels such as those in Clark County, but merely pointed out that at sufficiently high doses, perchlorate has the potential to cause fetal hypothyroidism and neurobehavioral disorders in children. This issue was considered by our peer reviewers, who did not disagree with our interpretation of potential health sequelae.

Comment 4: "The workplace/occupational studies demonstrated that the exposure encountered in the workplace may be above the no-effect level but are below the no adverse effect level. Environmental studies in the United States and Chile have found perchlorate concentrations below the no effect level, while regulatory proposals hover at orders of magnitude below even these low levels."

Response 4: OEHHA believes the studies mentioned by the commenters are informative, but not suitable for dose-response characterization. The limitations of some of these studies are discussed in the perchlorate risk assessment. Our UC peer reviewers supported our opinion that these studies were not appropriate for the quantitative risk assessment.

Combined comments submitted by Michael Girard, Perchlorate Study Group

Among the fifteen sets of comments submitted by Michael Girard, six sets were previously submitted during the external public review period of the first public review draft. As responses to those comments have been provided earlier, they are not repeated here. New major comments from five reviewers are provided.

Four sets of comments raised concerns on how some of the animal toxicity studies were conducted and how the results were interpreted. OEHHA shares some of the concerns, but stresses that the animal toxicity data were mainly used to understand the mode of action of perchlorate. Detailed dose-response evaluation was not carried out for some of the animal toxicity studies. These comment are not germane

to our final risk assessment, and no formal responses have been included here. Quantitative dose-response evaluation was based on human data in the final perchlorate risk assessment.

(a) InterTox, Incorporated

Comment 1: "At the core of the Draft RA is the conclusion that the "inhibitory effect of perchlorate on the uptake of iodide by the thyroid gland" is the "critical event for assessing perchlorate risk" or level of relevant "adverse health effect." In addition, the Draft RA states that "adverse health effects associated with low-dose perchlorate exposure are expected to be similar to those caused by iodine deficiency" (Draft RA, p. 1). Both conclusions are scientifically invalid and contradict decades of scientific research on the physiology of the thyroid gland. First, iodide uptake inhibition is not adverse, but rather is a reversible, mundane, and everyday occurrence of no biological consequence. Second, there is no scientific basis to expect perchlorate exposure to mimic iodide deficiency. Finally, California is not iodine deficient, so any conclusions based on effects that do or might occur in an iodine deficient population are irrelevant. OEHHA proposes to rely on these scientifically invalid conclusions to establish a PHG that is not scientifically defensible and hence contrary to California's statutory requirements found in Health and Safety Code § 116365 (c))(1)."

Response 1: In the final perchlorate PHG document, the inhibition of thyroidal iodide uptake is identified as the critical endpoint for dose-response characterization. OEHHA acknowledges there is a safety margin between NIS inhibition and other adverse health effects as a consequence of thyroid hormone disruption. However, the size of this safety margin is expected to vary depending on dietary iodine intake level and amount of iodine stored in the thyroid. Reviewers of the second University of California peer review (OEHHA, 2004) generally support OEHHA's approach and the identification of the study reported by Greer *et al.* (2002) as the critical study for quantitative dose-response evaluation.

OEHHA disagrees with the statement that there is no scientific basis to expect perchlorate exposure to mimic iodide deficiency. Based on the human and animal toxicity data available, the mode of action of perchlorate is believed to be the reduction of thyroidal iodide uptake. Iodine is the rate-limiting step in the synthesis of thyroid hormones. Both iodine deficiency and perchlorate exposure can lead to a less-than-optimal level of iodine for thyroid hormone synthesis, and therefore to disruption of thyroid functions.

Based on the available data, there is no evidence that the California population is iodine deficient. However, this does not exclude the possibility that a small percentage of the population is getting less than optimal iodine from the diet. Due to the increased need of iodine in pregnant women compared to the general population, women in pregnancy are more likely to get less than the optimal level of iodine. OEHHA does not agree that discussion of adverse effects related to various degrees of iodine deficiency is irrelevant. Severity of adverse effects is expected to be related to the degree and duration of exposure to perchlorate as well as the iodine status of the individual.

OEHHA agrees that competitive inhibition of iodine uptake into the thyroid (i.e., by nitrate and thiocyanate) is a common occurrence, but does not agree that such effects are therefore "of no biological consequence," as is abundantly reflected in the literature on endemic goiter associated with foods.

Comment 2: "The NOAEL for healthy men and women is at least 0.5 mg/kg-day (or 17,500 ppb). This level could be much higher, but we do not know how much higher because there appear to be no data revealing the point at which thyroid hormones first begin to decline." *The commenter also stated:* "Greer *et al.* (2002) derived estimates of a true no-effect level (NEL) for perchlorate in the range of 180 to 220 ppb in drinking water. … A NOEL is, by definition, fully protective of every member of the population with a built-in margin of safety. An exposure level too low to cause *any* biochemical effect is clearly too low to cause an *adverse* effect."

Response 2: OEHHA generally does not explicitly distinguish between a NOAEL and a NOEL for the PHG program, but considers the type and severity of effect in the choice of uncertainty factors.

The "NOAEL" cited by the commenter is derived from the highest dose (0.5 mg/kg-day) used in the Greer *et al.* study. At this dosage, Greer *et al.* observed close to 70 percent reduction in thyroidal iodide uptake in the exposed individuals. OEHHA disagrees with the suggestion that such an exposure would have no effect, especially if chronic. Based on the presently available data, OEHHA believes that the Greer *et al.* study is the one that is most suitable for quantitative dose-response assessment.

OEHHA does not agree that, "A NOEL is, by definition, fully protective of every member of the population with a built-in margin of safety." A NOEL is simply the dose below the lowest dose observed to have a statistically significant effect *in the study group, under the study conditions*. The NOEL does not include any measure of population variability except to the extent that, the greater the sample variability, the *less* likely that a statistically significant difference will be found. On the other hand, the BMDL method used by OEHHA explicitly accounts for variability within the study group, to derive a statistically-based minimal effect level in the sample population.

In the Greer *et al*. case, the 37 volunteers in the study were healthy, iodine-sufficient adults. Because of the small sample size, the variability in the Greer *et al.* data is likely to be much smaller than that in the general population. Sensitive subgroups, such as pregnant women with marginal iodine deficiency, infants, and individuals with thyroid problems, were not included in the study. In the perchlorate risk assessment, OEHHA applied an uncertainty factor of 10 to account for interindividual variability.

Comment 3: "Specifically, OEHHA has misinterpreted iodide uptake inhibition as adverse even though there is nothing at all adverse about it. OEHHA then compounds this error by applying a composite uncertainty factor of 30—60 if rounding is taken into account—that is totally inappropriate where the point of departure is itself non-adverse."

Response 3: In the development of the PHG, OEHHA identified iodide uptake inhibition as the critical endpoint for dose-response evaluation because it is the most readily

quantifiable effect of perchlorate. OEHHA acknowledges the existence of an inherent safety margin between the NIS inhibition and effects related to thyroid hormone disruption. However, the size of the safety margin is likely to vary in a heterogeneous population, and data are presently unavailable to assess the magnitude of this additional factor. Based in part on the recommendation of the reviewers in the second University of California peer review, OEHHA no longer applies an uncertainty factor of 3 for database limitation. The overall uncertainty factor used in the final risk assessment is 10, based on inhibition of iodide uptake.

Comment 4: "The magnitude of dietary nitrate exposure is well known. Much of it comes from green, leafy vegetables. When adjustments are made for both the higher quantity of nitrate and the potency of perchlorate, the potential for iodide uptake inhibition from nitrate delivered by single servings of common foods exceeds by orders of magnitude that which might occur from perchlorate at current environmental exposure levels."

Response 4: OEHHA is not aware of any study linking thyroidal iodide uptake inhibition with the consumption of green leafy vegetables. It is also not clear if individuals are consuming amounts of nitrate in a normal diet that reduce thyroidal iodine uptake. In a human study reported by Lambers *et al.* (2000), ten volunteers on an iodine-restricted and low-nitrate diet were exposed to 11 mg nitrate/kg-day (approximately 770 mg/day) for 28 days and did not experience any inhibition of thyroidal iodide uptake.

Comment 5: *The commenter compared the consumption of vegetables (with nitrate) to the ingestion of perchlorate contaminated water, and stated,* "What the comparison does illustrate, however, is that iodide uptake inhibition cannot be an adverse effect because it appears to occur with every meal. It is scientifically indefensible to conclude, as OEHHA implicitly has done, that this biochemical phenomenon is adverse when it occurs regularly and normally as a part of everyday living."

Response 5: OEHHA has not seen scientific data supporting the claim that consumption of vegetables would lead to NIS inhibition, and that iodide uptake inhibition "occurs with every meal." The commenter also did not specify the degree of NIS inhibition that is to be expected from vegetable consumption, and evidence that consumption of vegetables with high levels of nitrate is without physiological effects on the thyroid.

Comment 6: "Thyroid hormone and TSH levels in the human body are not constant: mundane factors influence daily concentrations. Submitted comments note that such factors include time of day, stress, and temperature change (Bruce *et al.*, 2002b) and the presence of environmental goitrogens in the diet, including thiocyanate-like substances in soy products and nitrate (Engel and Lamm, 2002). The body naturally adjusts to these phenomena through "homeostasis": the hypothalamus and pituitary gland detect changes in T4 and triggers greater production of TSH. This causes thyroid hormone levels to return to normal. As comments by Goodman (2003a) state, "…small fluctuations in serum T4 are not physiologically meaningful…Studies of various environmental

influences (including climate, season, altitude, time zone, and exercise) in humans have demonstrated that homeostasis mechanisms allow T4 and TSH levels to vary substantially over a range of environmental conditions."

Response 6: OEHHA is aware of the normal fluctuations in thyroid hormone and TSH levels, and that the body has a certain capacity to cope with stresses on the thyroid hormone system. One concern is that continuous exposure to perchlorate at a sufficiently high dose may cause an imbalance of a system that is already under stress (e.g., due to marginal iodine deficiency or pregnancy). Another concern is that fetuses and infants have relatively little thyroid hormones stored in their thyroids and they are less capable than adults to adjust to the additional stress on the thyroid.

Comment 7: "The Draft RA uses a relative source contribution of 80 percent. These adjustments are typically made to derive safe drinking water levels. However, such adjustments are scientifically appropriate only when the target endpoint is a true adverse effect. Because iodide uptake inhibition is not adverse, there is no scientific justification for any relative source contribution in this case."

Response 7: The RSC is based on estimated exposures, not effects. Since the release of the second public review draft, perchlorate has been detected in lettuce, cucumbers, strawberries, cow's milk and breast milk. Due to these findings, the relative source contribution has been changed to 60 percent in the final PHG document.

Comment 8: "The Draft RA cites two ecological epidemiological studies (Schwartz, 2002; Brechner *et al.*, 2000) as support for the assertion that low dose perchlorate exposure may be associated with adverse health effects. No other studies have made these assertions. However, a number of comments have cited weaknesses in these studies that make these conclusions suspect."

Response 8: In the PHG document, OEHHA reviewed and discussed positive as well as negative epidemiological studies related to perchlorate. The studies reported by Schwartz (2002) and Brechner *et al.* (2000) shared some of the shortcomings and limitations of the other (negative) ecological studies, and none of these are used in the final document for the quantitative risk assessment.

Comment 9: "Although the Draft RA is based on human studies, the document refers at several points to animal developmental studies as supportive. However, the relevance of the animal studies has been questioned." *The commenter criticized the design and implementation of a number of animal toxicity studies, including the suggestion that soybean products in the rodent chow might have confounded some of the study results.*

Response 9: OEHHA recognizes some of the challenges in interpreting the animal toxicity data. Overall, the animal data support the mode of action of perchlorate described in the risk assessment, and indicate low adverse effect levels. It may be difficult to quantitatively extrapolate some of the findings in rat to humans due to the difference in sensitivity to thyroid hormone disruption, but OEHHA believes that the

animal data is supportive of the human data. OEHHA chose the human data reported by Greer *et al.* (2002) for dose-response evaluation.

The commenter did not provide sufficient information on dietary factors in the rat studies to judge their possible contribution to the adverse effects described.

Comment 10: "At issue is the Draft RA hypothesis that ambient perchlorate exposures cause adverse thyroidal effects in pregnant women and their offspring that are significantly different from those that occur normally during pregnancy. Because data showing adverse thyroidal effects in perchlorate exposed populations are lacking, the Draft RA cites a number of studies describing adverse thyroidal effects (goiter) in iodine deficient or hypothyroid populations. Comments by Borak note that supporting studies cited in the Draft RA pertain to populations with moderate to severe iodine deficiency, or populations in which iodine status is not reported (Borak, 2002; 2003). Lamm (2003) adds that this literature demonstrates that adverse thyroidal effects are not seen in pregnancy in iodine-sufficient populations. These studies are only relevant to environmental perchlorate exposures in that they indicate that pregnancy should not have an adverse thyroidal effect on mothers in the U.S. and California populations that are iodine sufficient."

Response 10: The major goal of the PHG program is to estimate contaminant levels in drinking water that are not likely to cause any adverse health effects in individuals, including sensitive subpopulations, that consume the water for a lifetime. OEHHA believes that the amount of exposure to perchlorate and the severity of iodine deficiency would be related to the severity and nature of any adverse health effects. However, in our opinion, the current scientific database does not allow a dose-response evaluation with the degree of certainty implied in the comment above. For this reason, OEHHA has included a significant, though relatively small, uncertainty factor in the risk assessment for the PHG. We have specifically addressed the comments of Drs. Borak and Lamm elsewhere in these responses to comments.

Comment 11: "The Draft RA has proposed three possible sensitive sub-populations: (1) the developing fetus; (2) the pregnant female; and (3) pregnant women with autoimmune thyroiditis. OEHHA has no supporting scientific evidence of effect in any of these subpopulations at exposure levels of current concern. With respect to the developing fetus, the best scientific information is that the mother provides thyroidal function for the first half of gestation (Lamm, 2003; Goodman, 2003a). If the perchlorate level is insufficient to affect maternal thyroxine output, it cannot affect the fetus by blocking thyroxine synthesis. With respect to the adult female thyroid, particularly of the pregnant female, minor shifts in thyroidal iodide uptake in an iodine-sufficient population will not affect maternal thyroidal output. Finally, there may be a sub-population of pregnant women with autoimmune thyroiditis that adversely affects the fetus, but this problem is related to anti-thyroidal antibodies that cross the placenta independent of iodine supply."

Response 11: Due to physiological, dietary, or behavioral differences (such as smoking), some individuals are more likely to have less than the optimal amount of iodine. Based

on the National Academy of Sciences recommendations (NAS, 2001) (see table below), the need for iodine is higher in pregnant and lactating women than in non-pregnant women. For this reason, pregnant women and their fetuses, lactating women, and infants who are breast-fed are identified as sensitive populations in the final risk assessment.

Estimated iodine requirement for adult women (NAS, 2001)

	Estimated Average Requirement (µg/day)	Recommended Dietary Allowance (µg/day)
Women (ages 19 years and older)	95	150
Pregnant women (14-50 years)	160	220
Lactating women (14-50 years)	209	290

In addition, individuals with thyroid problems are also identified as a sensitive subpopulation. The perchlorate PHG is designed to protect not only the general population but also these sensitive subpopulations.

OEHHA agrees with the commenter that maternal thyroxine output and normal fetal development are not likely to be affected by perchlorate exposure at the level designated as the PHG. The basis for the PHG is the concern that a sustained reduction in thyroidal iodide uptake in a pregnant woman who is getting less than optimal amount of iodine may lead to some undesirable health effects in the mother as well as the fetus. The commenter suggests that perchlorate would only affect the maternal thyroid. However, several other effects must be considered, including inhibition of iodide uptake into the placenta, transport of perchlorate across the placenta, direct effects of perchlorate on the fetal thyroid, decreased iodide in breast milk, and perchlorate secreted in the milk. Based on the PBPK modeling of the distribution of perchlorate in rat, Clewell *et al.* (2003) predicted the fetal rat thyroid is more sensitive to NIS inhibition by perchlorate than the adult rat, the pregnant rat, and the neonatal rat.

(b) Comments from Jonathan Borak, Jonathan Borak & Company, Inc.

Comment 1: "[T]here is positive evidence of a margin of safety that indicates the extent to which thyroid iodine uptake can be inhibited before alterations in thyroid function manifest. We expect that others, using statistical models and benchmark dose calculations, will estimate this margin of safety to be 10-100 fold. It is our impression that that is a correct order of magnitude; for sake of brevity we do not present the calculations here. In summary, we believe that by regarding the inhibition of iodine uptake as a NOAEL, rather than a NOEL, OEHHA has disregarded a margin of safety at least 10-fold in magnitude."

Response 1: OEHHA calls the inhibition of iodine uptake an undesirable effect of perchlorate exposure, and agrees that there is likely to be a safety margin between the NIS inhibition and the impairment of thyroid functions. However, the size of this safety margin is assumed to vary among individuals depending on the dietary iodine intake and

amount of iodine stored in the thyroid, among other things. OEHHA has not seen evidence that there is a safety margin of 10-100-fold which is applicable to all individuals, including sensitive subpopulations. However, we consider that the minimal uncertainty factor of 10 that we have used in development of the perchlorate PHG is consistent with the nature of the endpoint, inhibition of iodine uptake.

Comment 2: "It is true that individuals with sufficiently severe iodine deficiency suffer hypothyroidism and consequent developmental deficits, and it may be true that individuals exposed to massive perchlorate doses suffer conditions that mimic iodine deficiency, but there is no evidence that such effects are relevant to those with "perchlorate exposure in the low dose range". Thus, we find no basis for the Draft contention that one can learn about low-dose perchlorate toxicity by studying iodine-deficient or hypothyroid individuals. As the previous point, the issue is one of dose. There is a substantial margin of safety between "perchlorate exposure in the low dose range" and that dosage required to induce iodine deficiency and thyroid perturbation. The OEHHA PHG fails to consider that margin of safety."

Response 2: The statement, "As perchlorate competitively blocks iodide from entering the thyroid gland, many of the adverse effects of perchlorate exposure in the low dose range are similar to those of iodine deficiency" is intended to distinguish some of the adverse effects (e.g., blood disorder) of perchlorate that are only relevant at very high doses.

OEHHA agrees that the issue is one of dose. OEHHA has considered the safety margin inherent in the nature of the critical endpoint. However, the size of the margin is difficult to determine and is likely to vary among individuals in a population. This is one of the reasons that in the final perchlorate risk assessment, an overall uncertainty factor of 10, based on protection of pregnant women and their fetuses, is used in the determination of the PHG.

Comment 3: "The Draft argues that a sizeable number of US pregnant women have inadequate iodine intake, an argument based on data from NHANES III as cited in Hollowell *et al*. (10). But, the Draft probably exaggerates and perhaps misrepresents the iodine sufficiency of the US population generally and that of pregnant women specifically."

Response 3: The document has been revised to indicate that based on the NHANES III data, there is no evidence that the general U.S. population is suffering from iodine deficiency.

Comment 4: *The commenter disagreed with OEHHA on the interpretation of a number of studies that linked iodine deficiency during pregnancy or impaired maternal thyroid functions with adverse neuropsychological development of the child, and also said,* "At issue is the likelihood that ambient perchlorate exposures cause effects in pregnant women and their fetuses that are significantly different from those that occur normally during pregnancy. OEHHA proposes that such perchlorate induced effects can be

expected, but little or no supporting evidence is provided. Instead, the Draft points to studies describing adverse effects in settings distinguished by severe iodine deficiency and/or significant maternal hypothyroidism. The relevance of such grossly abnormal situations to the more subtle effects of ambient perchlorate exposure is neither obvious nor certain."

Response 4: The severity of adverse health effects would undoubtedly be related to the severity of iodine deficiency and hypothyroidism. The toxicology of perchlorate is sufficiently well understood to predict that at high doses, perchlorate could induce thyroid enlargement in pregnant women with marginal iodine deficiency and cause abnormal brain development in their fetuses. The prediction is based on current knowledge about the mode of action of perchlorate and adverse effects associated with hypothyroidism in humans (Heyerdahl *et al.*, 1991; Heyerdahl, 2001; Rovet *et al*., 1987; Rovet, 2000; Song and Rovet, 2001). However, a dose-response characterization of such effects is not possible at this time due to the lack of human toxicokinetic data and large interindividual variability. Because perchlorate reduces thyroidal iodide uptake, it is reasoned that if one can prevent this well-known effect from happening, then all subsequent or higher-dose effects related to thyroid hormone disruption would be prevented.

Comment 5: "The only thyroid change consistently associated with mild-moderate iodine deficiency was increased thyroid volume, but increased volume (albeit less marked) was also noted in controls and iodine-supplemented women. It is difficult to imagine that such changes that are generally reversible and primarily related to placental hCG, rather than iodine intake, is an appropriate "critical effect" for a PHG."

Response 5: OEHHA believes thyroid enlargement during pregnancy is a thyroidal stress-related effect that should be avoided. It is not appropriate to attribute thyroid enlargement during pregnancy to placental hCG alone as it does not occur in women that are iodine-replete, and administration of iodine supplement can prevent it from happening (NAS, 2001).

Comment 6: "Based on the lack of evidence provided in the Draft, as well as the statement that the effects of breast feeding "is considered covered in the limited data uncertainty factor", we recommend that OEHHA delete the following sentence from page 76: "Two other possible sensitive sub-populations are the infants and elder people with existing thyroid problems" (Draft, p. 76)."

Response 6: Individuals that are identified as sensitive subgroups are believed to be more sensitive or susceptible to the effects of exposure relative to the general population. OEHHA believes there are reasons to retain infants and individuals with thyroid problems as sensitive subpopulations. Based on the recommendation from the second University of California peer review (OEHHA, 2004), OEHHA no longer applies an uncertainty factor for data limitation in the final risk assessment.

Comment 7: “The Draft provides little or no evidence in support of its definitions of "sensitive sub-populations". These groups have been identified as hypothetically sensitive on the basis of observations made of individuals suffering moderate-severe iodine deficiency and/or frank hypothyroidism. The failure to document such effects in borderline or mildly iodine deficient individuals is evidence that there is a significant margin of safety between the perchlorate levels of concern here and the levels likely to cause any of the contemplated adverse effects in even such "sensitive sub-populations".

Response 7: It is generally recognized that the U.S. population is iodine replete. As the need for iodine is estimated to be almost 70 percent greater (NAS, 2001) in pregnant women than in non-pregnant women, there is a greater chance of a pregnant woman to be getting less than optimal iodine. The sensitive subpopulations are identified based on what we know about the mode of action of perchlorate and the adverse health effects associated with various degrees of iodine deficiency. Two out of three reviewers of the second University of California peer review (OEHHA, 2004) agreed with OEHHA on this issue. The other reviewer did not comment on the identification of sensitive subpopulations.

Comment 8: “The Draft depends on insufficient and unreliable data to generate its RSC. First, there is no survey data indicating that perchlorate accumulates in lettuce or other foods under normal field conditions. Second, the Draft has relied solely upon data from a single non-peer reviewed experiment, in disregard for the limitations and cautions stressed by the US EPA authors and reviewers about such misuse of those data, in order to calculate an RSC. Finally, even if the estimated levels of perchlorate in lettuce were as calculated in the Draft (but there is no evidence that that is so), the Draft has still overstated the average daily consumption of lettuce and, thereby has also overstated the predicted daily consumption of perchlorate. There is no scientific basis to propose an RSC less than 100%, because there is no scientific evidence that consumption of food is a significant exposure source of perchlorate.”

Response 8: Since the release of the draft risk assessment, a number of studies have shown perchlorate contamination of foods, including lettuce, cucumber, strawberry, grass, and cow’s milk. With significant but nonquantifiable sources of exposure to perchlorate other than drinking water, prudence requires an RSC less than the default maximum of 0.8. Although an RSC of 0.2 would likely by used by the U.S. EPA in this case, OEHHA believes the limited data are more consistent with a larger value. The relative source contribution is assumed to be 60 percent in the final PHG document.

Comment 9: “The Schwartz study is based on a flawed exposure assessment that is almost certainly incomplete and inconsistent, that assigns arithmetically manipulated exposure levels without any explanation of the methods employed, and that suffers from significant misclassification. OEHHA cannot rely upon this study as support for its PHG. Although appropriate to consider and discuss the study in the Draft's literature review (i.e., pages 37-42), it should not be cited or discussed in the Risk Characterization. Accordingly the following statement should be deleted from page 77: "There is an

ecological study indicating that a low level of perchlorate in drinking water was correlate with thyroid hormone perturbation in newborns (Schwartz, 2001)" (Draft, p. 77)."

Response 9: We agree that there are significant limitations to this study, but think that it is appropriate to cite both the positive and negative ecological studies in the Risk Characterization. The discussion has been slightly reworded.

Comment 10: "Glinoer *et al.* (26) compared maternal to fetal thyroid function by means of the maternal thyroid data described above and test results from cord blood. The Draft improperly describes the study population, by merely quoting the abstract, which described the population as "marginal iodide supply (less than 100 µg/day in 80 percent of women)". But this is the exact same population of women as described in the prior report that had median urine iodine levels of 45-50 µg/L."

Response 10: These two descriptions are not inconsistent. Glinoer *et al.* (1992) said the maternal and neonatal thyroid function study was carried out in an area with a marginal iodine supply (less than 100 µg/day in 80 percent of women). In a previous paper, Glinoer *et al.* (1990) reported that the median urinary iodine concentration of these women were 50 µg/L and 45 µg/L during the first and second halves of gestation. What is important is that all women were screened at the beginning of the study and none of them had detectable thyroid abnormality. Pregnancy and iodine deficiency together increased the incidence of thyroid problems in these women.

Comment 11: "Smyth *et al.* (28) evaluated thyroid volume in pregnant women during each of three trimesters, but study subjects were not studied longitudinally (each trimester a different group of women were selected). The Draft states that the mean urinary iodine excretion was 82 µg/day, but the study actually reports median urinary iodine as follows: non-pregnant = 80 µg/L; first trimester = 148 µg/L; third trimester = 132 µg/L. Thus, given the nonlongitudinal design, it is not possible to determine whether the pregnant women were iodine sufficient or deficient. Thyroid function was not studied. Thyroid volume increased throughout pregnancy, a finding consistent with those described by Burrow *et al.* (23) during normal pregnancy. The relevance of this study to issues of iodine deficiency or perchlorate exposure is unclear."

Response 11: There were two groups of pregnant women in the study. The 115 women in Group A were selected opportunistically. There were about 30 to 40 women in each of the trimesters and each trimester's study group was comprised of different individuals. Group B consisted of 38 women who were followed during the 3 trimesters of pregnancy and at approximately 6 weeks postpartum. Thyroid ultrasound scans were made on 20 of these women during each trimester of pregnancy. The observed changes in urinary iodine excretion and thyroid volume were similar in Group A and Group B. The mean thyroid volume of the nonpregnant women was 11.3 mL, consistently lower than the 14 mL, 17 mL, 17 mL measured during the first, second, and third trimesters, respectively, of the women in Group B.

The median urinary iodine excretion was 70 µg/L in the nonpregnant controls, while the median urinary iodine excretion was 160, 120, and 110 µg/L for the Group B women

during the first, second, and third trimesters, respectively. Similarly elevated urinary iodine excretion was also observed in the Group A women. In addition, Smyth *et al.* (1997) noted that the drastic drop in urinary iodine excretion 3 days after delivery observed in the Group A women indicates a direct effect of pregnancy on urinary iodine excretion. They suggested that in the absence of increased dietary iodine intake, pregnant women in an area of moderate dietary iodine intake (median urinary iodine of 82 µg/L) would be in negative iodine balance. This study shows pregnant women with less than optimal iodine intake are more susceptible to thyroid enlargement than the general population.

(c) Comment from Monte A. Greer, Oregon Health Sciences University

Comment 1: *Based on past experience in treating hyperthyroidism, the commenter pointed out that different drugs showed higher or lower potency in humans than in rats. The commenter suggested that,* "...although basic hypothalamic-pituitary-thyroid physiology and pharmacology are similar, one cannot predict quantitative relationships in one species from studies in another."

Response 1: OEHHA understands the difficulties in extrapolating dose-response information from one species to another. In the PHG risk assessment, the dose-response evaluation was based on a human study.

(*d) Comment from Steven H. Lamm, Consultants in Epidemiology and Occupational Health, Inc.*

Comment 1: *The commenter criticized the study reported by Brechner et al. (2000) and listed some of the limitations of the study.*

Response 1: OEHHA is aware of the study limitations and they are discussed in the perchlorate risk assessment.

(e) Comment from Steven H. Lamm and Offie P. Soldin, Consultants in Epidemiology and Occupational Health, Inc.

Comment 1: *The commenters criticized the study reported by Schwartz (2001) and listed some of the limitations of the study.*

Response 1: OEHHA is aware of the study limitations and they are discussed in the perchlorate risk assessment.

Comments from Gay Goodman, Intertox, Inc.

Comment 1: *Using some unpublished data in the study reported by Greer et al. (2002), the commenter modeled the relative thyroidal iodide uptake ratio (uptake measured after perchlorate exposure/uptake measured before perchlorate exposure) for interindividual relative differences in iodine excretion at baseline (before perchlorate exposure). In addition, the intraindividual relative changes in iodine excretion between the baseline and after 14-day exposure to perchlorate were also modeled. Based on the findings of these models, the commenter suggested that subjects in the lowest baseline iodine excretion category (mean=97 µg/day) were less sensitive to the perchlorate inhibition of iodide intake those in higher baseline iodine excretion categories (mean 197, 314, and 531 µg/day). It was further suggested that persons at the low end of dietary iodine intake have a higher threshold for perchlorate inhibition of thyroidal iodide uptake than persons with higher iodine intake.*

Response 1: The applicability of the findings modeled to the general population is questionable because of the small sample size, and the limited urinary iodine measurements per subject. The spot urinary iodine samples may not reflect the iodine status of the person, as was pointed out by several commenters with regard to the NHANES III data.

This finding appears to be at odds with the modeling results submitted to OEHHA by Richard B. Rothman. In his comments to the first public review draft, Dr. Rothman concluded that "because plasma iodide levels are very low compared to its Km for the NIS, the perchlorate NOEL will not be changed by conceivable changes in plasma iodide or dietary intake of iodide." "Regulatory mechanisms that either increase or decrease NIS availability will also not change the perchlorate NOEL." At present, data are insufficient to resolve this disagreement.

Comments from Deborah Proctor, Exponent Corporation

Comment 1: "A less stringent uncertainty factor, such as a factor of 3, would be sufficient to account for susceptible subpopulations in the U.S. because 1) iodide deficiency is not observed in the U.S. and dietary iodide is sufficient in the U.S. to protect against adverse health effects in the mother or fetus, 2) epidemiologic studies do not show thyroid decrements in infants or children exposed to relatively high concentrations of perchlorate in drinking water, and 3) infants with congenital hypothyroidism or insufficient thyroid hormone levels are tested and treated at birth and therefore, would not be anticipated as a population susceptible to the effects of perchlorate."

Response 1: Based on the NHANES III data, the population of the U.S. as a whole is not believed to suffer from iodine deficiency. However, the NHANE III data cannot exclude the possibility that a small percentage of the population gets less than optimal iodine from the diet. Due to the increased need of iodine in pregnant women, compared to the general population, women in pregnancy are more likely to get less than the optimal level of iodine. This is one of the reasons why pregnant women and fetuses are identified as sensitive populations.

The Crump *et al.* (2000) study showed that thyroid functions of neonates and schoolchildren exposed to 110 ppb perchlorate in drinking water were not significantly different from those living in control areas. The interpretation of this study is complicated by the observations of relatively high urinary iodine levels (mean ranged from 61 to 77 µg/dL) and high prevalence of goiter in the exposed as well as unexposed children. It has been suggested the study might have been confounded by exposures to nitrate. Furthermore, the tests used in the study would not be able to detect changes in maternal and fetal thyroid hormone levels during the gestation period.

Comment 2: "Many of the studies that OEHHA relied upon were conducted in other countries, where iodide uptake from the diet is low or inadequate. Thus, given that iodide intake of participants in these studies may not be comparable to dietary iodide in the U.S., the reported effects on the thyroid also may not be comparable to pregnant women in the U.S."

Response 2: OEHHA agrees that in general the dietary iodide intake of pregnant women in the U.S. is sufficient and is higher than most of the studies cited in the risk assessment. The purpose of describing these studies in the risk assessment is to show the association between iodine deficiency during pregnancy and thyroid enlargement as well as impaired fetal brain development. The nature and the severity of adverse health effects are related to the severity of iodine deficiency.

Comment 3: *The commenter suggested that it is not necessary to apply an uncertainty factor of 3 for the short exposure duration of the Greer et al. (2002) study because (a) competitive inhibition of NIS is the mode of action and it can account for all known toxicity of perchlorate, and (b) Lamm et al. (1999) demonstrated that human thyroid function was unaffected following prolonged exposure (5+ years) to perchlorate levels as high as 0.5 mg/kg-day.*

Response 3: A number of adverse health effects associated with high doses of perchlorate have been reported in clinical studies. These effects are not believed to be mediated through the perturbation of thyroid hormones. The workers in the occupational study reported by Lamm *et al.* (1999) were exposed to perchlorate in air on an intermittent basis. It has been shown that during the "off" days, there was little or no perchlorate in the system. Replenishment of thyroidal iodide was possible during that time. There are difficulties in extrapolating this study result to the general population where exposure to perchlorate in drinking water is likely to be continuous.

We agree that an uncertainty factor of 3 is not needed to account for short exposure duration and database limitation, and this is not applied in the final perchlorate risk assessment.

Comment 4: *The commenter recommended that the benchmark dose approach be used to determine a point of departure (POD) in the development of a perchlorate PHG, and suggested that the benchmark dose response of two standard deviations from the mean of the control group (BMDL of 0.033 mg/kg-day) be used as the POD.*

Response 4: There are a number of scientific judgments in defining the point of departure for continuous data. OEHHA realizes there are alternatives to the approach described in the PHG document, but points out that there is no control group in the Greer *et al.* study. The lowest dose group was given a perchlorate dose of 0.007 mg/kg-day. Also, the BMDL (0.033 mg/kg-day) suggested by the commenter is higher than the second lowest dose group (0.02 mg/kg-day). Greer *et al.* reported approximately 16 percent thyroidal iodide uptake inhibition in this dose group after 14 days of exposure.

Comment 5: "At least in California, it is not likely that air, soil or food is a significant source for exposure to perchlorate. Therefore, applying a source contribution factor of 100% for perchlorate in drinking water would be appropriate for deriving a PHG for perchlorate."

Response 5: Recently published sampling data indicate that perchlorate is taken up by farm produce such as lettuce, cucumber, and strawberry. In addition, perchlorate has also been detected in several samples of cow's milk and one of human breast milk. In the final document, a relative source contribution of 60 percent (0.6) is used for the development of a perchlorate PHG.

Comments from Renee Sharp, Environmental Working Group

Comment 1: *Center for Community Action and Environmental Justice, Clean Water Action, the Environmental Working Group, and Physicians for Social Responsibility Los Angeles expressed their strong support for the endpoint OEHHA uses to calculate the perchlorate PHG. It was stated that* "there is no endpoint other than the inhibition of iodide uptake that could be used justifiably given OEHHA's decision to base its PHG on Greer *et al.* (2002), a short-term study conducted on healthy euthyroid adults. ... It is likely that changes in thyroid hormones levels would be seen if the study length were extended since inhibition of iodide uptake by the thyroid was seen at all doses tested. But more importantly, the study was not conducted on the populations of concern, namely pregnant women, fetuses, infants and children who are almost certain to be more susceptible to the effects of perchlorate."

Response 1: No response required.

Comment 2: *The commenter suggested that the benchmark dose approach should be used for the development of the PHG* "...given the extremely small sample sizes in the Greer study, the related power issues, and the large amount of interindividual variability expected in the general population in response to perchlorate exposure, in this case BMD is clearly superior to the NOAEL-based approach and should be used in calculating the final PHG."

Response 2: Based on the external comments and the recommendation of the second University of California peer review, OEHHA applied the benchmark dose approach in evaluating the thyroidal iodide uptake data reported by Greer *et al.* (2002) in the final

PHG document.

Comment 3: "...it is important for OEHHA to more explicitly base the perchlorate PHG on infant exposures since these exposures are four times greater relative to that of adults and infants are known to be "particularly sensitive to iodine deficiency." And using a lower uncertainty factor is unjustifiable given that no data exists on how an infant thyroid might respond to perchlorate."

Response 3: The fluid consumption/body weight ratio of infants is 4-6 times larger than that of pregnant women or adults. Clewell *et al.* (2003) modeled the absorption, distribution, and excretion of perchlorate in adult rat, pregnant rat, fetal rat, neonatal rat, and lactating rat, and predicted that perchlorate dose, measured as the area under the curve of perchlorate in blood, of the neonatal rat is not higher than that of the pregnant rat or the adult rat. Also, based on their PBPK modeling results, the fetal thyroid has a higher sensitivity to the inhibitory effect of perchlorate on thyroidal iodide uptake than that of other rat groups. A similar conclusion has been reached by U.S. EPA. For the final PHG, OEHHA provides health-protective assessments for both the fetuses of pregnant women and infants.

Comment 4: *The commenter recommended an uncertainty factor of* "at least 300*," and cited several reasons, namely: (I) limitations of the Greer et al. study, (ii) higher sensitivity to the effects of perchlorate in the populations of concern, (iii) infants have a greater need (7 to 15 times more) for iodine than adults, (iv) unlike the maternal thyroid, the fetal thyroid is unable to increase thyroidal iodide uptake as an adaptive response to a decrease in iodine supply, (v) concentration of perchlorate in breast milk, as reported by Yu et al. (2000), and (vi) the possibility of in utero programming of the hypothalamus-pituitary-thyroid axis (U.S. EPA, 2002).*

Response 4: The greater need for iodine by infants, pregnant women, and lactating women makes them more likely to be getting less than the optimal amount of iodine in the diet. The greater need does not necessarily translate into a lower threshold of thyroidal iodide uptake inhibition. The lack of adaptive capability of the fetal thyroid to a reduced iodine supply support the identification of the reduction of thyroidal iodide uptake as the critical end-point (Versloot *et al.*, 1997).

Yu *et al.* reported that perchlorate concentration in rat's breast milk is about twice as high as that in the maternal blood. Clewell *et al.* (2003) using PBPK modeling predicted that the perchlorate dose received by the neonatal rat is not higher than that of the lactating rat or the pregnant rat.

The possibility of in utero programming has been considered, but it is important to realize that the rat thyroid tumors were observed only in the highest dose group, 30 mg/kg-day. No thyroid tumors were observed in rat pups exposed in utero at dose groups of 0.3 mg/kg-day and 3 mg/kg-day. OEHHA agrees with the reviewers of the second University of California peer review, who recommended the elimination of the uncertainty factor for short exposure duration of the Greer *et al.* study and database limitation.

In view of the nature of the critical endpoint selected (i.e., reduction of thyroidal iodide uptake) and the inherent safety margin between this effect and disruption of thyroid hormone homeostasis, which is not explicitly included in the risk assessment, OEHHA applied an overall uncertainty factor of 10 for interindividual variability in the final risk assessment, based on protection of the fetus.

Comment 5: "[T]he proposed PHG range of 2 to 6 is the same or higher than the concentrations of perchlorate which have been associated with changes in infant thyroid hormone levels in two epidemiological studies in California and Arizona (Schwartz 2001, and Brechner *et al.* 2000)." *The commenter suggested that the margin of safety is effectively zero if the proposed PHG values were adopted.*

Response 5: Both positive and negative epidemiological studies related to perchlorate exposure and changes of TSH or T4 levels in neonates have been published. These studies suffered from the limitations inherent in ecological study design, including an inadequate control of confounding factors. Because of their limitations, OEHHA does not believe that a linkage has been established between low levels of perchlorate in drinking water and changes in neonatal serum T4 or TSH levels.

Comment 6: *New data has become available showing concentration of perchlorate in field-grown vegetables irrigated with contaminated water. A concentration factor as high as 65-fold has been estimated. Given that 90 percent of the nation's winter lettuce crop is irrigated by the contaminated Colorado River water at 6-9 ppb, it is possible that a member of the public could be getting more perchlorate from a salad than from the drinking water. A relative source contribution of 40 percent was recommended.*

Response 6: The recent detections of perchlorate in a number of crops, and in milk samples, substantiate the concern about multiple exposure sources. However, because of the limited number of samples analyzed, a quantitative evaluation cannot be performed. A relative source contribution of 60 percent is assumed in the final PHG document.

Comments from Annie M. Jarabek, National Center for Environmental Assessment, Office of Research and Development, U.S. EPA

Comment 1: "The PHG document never discusses the calculation by EPA of a human equivalent exposure (HEE) based on laboratory animal data from different life stages using physiologically-based pharmacokinetic (PBPK) models. This is an important omission. The HEE for the overall derivation was based on using the area-under-the-curve of blood perchlorate concentration as the dose metric. The HEE for the dams of the pups exposed *in utero* that showed thyroid and brain effects was also chosen."

Response 1: A discussion of the PBPK modeling results reported by Clewell *et al.* (2003a,b) has been added to the final PHG document. These results appear to be the basis for the conclusions reported in the U.S. EPA (2002) risk assessment.

Comment 2: *The commenter suggested that a NOAEL approach should not be used to analyze the Greer et al. (2002) data due to the small number of subjects at the low dose. It was stated that peer reviewers of U.S. EPA's perchlorate risk assessment also did not agree that the degree of iodide inhibition seen in the study should be viewed as a NOAEL. There were concerns about the duration of the study and the meaning of the magnitude of perturbations observed when viewed from a population perspective. It was suggested that healthy adult humans store thyroid hormones sufficient to supply several week's requirements even after blockage of the iodide uptake mechanism in the thyroid.*

Response 2: In the final perchlorate PHG, OEHHA applied only the benchmark dose approach for the quantitative dose-response evaluation. OEHHA agrees the inter-individual variability in the general population is likely to be larger than that indicated in the study data; for this reason, an uncertainty factor of 10 is used for intraspecies variability in the risk assessment.

Comment 3: "The PHG document incorrectly states on page 75 that the standard deviation is large because it reflects day-to-day intra-individual variability and inter-individual variability. Benchmark dose-response modeling is an empirical fitting exercise not mechanistic modeling. Consideration of that type of mechanistic variability and the limits of the Greer *et al.* (2002) study to account for them is best addressed with an uncertainty factor. The benchmark approach addresses only the lack of fit of the Hill equation to the dose-response of a set of subjects with limited sample size."

Response 3: The standard deviation calculated from the data is independent of the model. There can be arguments about the relative contributions of day-to-day intra-individual variability and interindividual variability to the standard deviation, but certainly both types of variability are present in the data set. We agree that an uncertainty factor should be applied to the results of the benchmark analysis, and have used a factor of 10 in the final PHG calculation for protecting the fetuses and pregnant women.

Comment 4: *The commenter agreed with OEHHA in the application of an uncertainty factor of 10 for intraspecies variability. It was suggested that in addition to the small sample size and the fact that the subjects were healthy in terms of thyroid function, many other factors, such as age distribution, health status, smoking habits, weight, and ethnicity might contribute to interindividual variability. It was also noted that the study of Greer et al. (2002) did not evaluate any neurological, developmental, neoplastic, or thyroid gland changes that may have resulted from changes in thyroid hormone.*

Response 4: If one believes that the neurological, developmental, neoplastic and thyroid gland changes observed in test animals are a result of thyroid hormone disruption, then preventing the initial event (reduction of thyroidal iodide uptake) will also prevent all subsequent adverse effects. This is the foundation of OEHHA's risk assessment of perchlorate.

Comment 5: "This Greer *et al.* (2002) study simply can not inform the dose-response for effects in the fetus. The fetus dosimetry must take into account the thyroid hormone status of the mother, that perchlorate crosses the placenta to inhibit the fetal thyroid, and that perchlorate not only inhibits iodide transfer into the milk but is itself transferred to the fetus via lactation."

Response 5: OEHHA believes that at or below the concentration specified by the PHG there should be no thyroidal iodide uptake reduction and no impact on the maternal thyroid function. Unless the NIS in the placenta behaves differently than that in the thyroid, there should also be no reduction of iodine transfer to the fetus. Using PBPK modeling, Clewell *et al*. (2003) predicted that the fetal rat thyroid is more sensitive to the inhibitory effect of perchlorate on thyroidal iodide uptake than the pregnant rat, lactating rat, and neonatal rat. It is not clear if this result can be extrapolated to humans. The 10-fold uncertainty factor helps to address this uncertainty.

It is also possible that perchlorate can be concentrated in breast milk, so that nursing infants might get a higher dose than the lactating mother. This concern is alleviated by three pieces of information: (a) using a PBPK model for rats, Clewell *et al.* (2003) predicted the perchlorate dose received by a neonatal rat is not higher than that of a lactating rat; (b) limited sampling data on cow and human milk showed levels of perchlorate which appeared to be in the same range as the water the mothers were drinking (Kirk *et al.*, 2003); and (c) clinical use of pertechnetate (TcO_4^-) showed that about 3-11 percent of the dose given to a nursing mother was secreted into the breast milk. Pertechnetate is structurally similar to perchlorate and may have a greater ability than perchlorate to inhibit iodide transport into thyroid tissues *in vitro*. A more detailed discussion of the subject is provided in the perchlorate risk assessment.

Comment 6: "With respect to a factor for duration, a clear trend in the data is evident with the effective perchlorate dose to inhibit uptake decreased on day 14. This argues for at least UF of 3 for duration considerations of the study design per se. With respect to database, as noted above, this NOAEL falls only slightly below where other endpoints suggest a LOAEL. Further, the 2002 peer panel agreed that the observation of tumors in young adult animals exposed *in utero* suggests that programming of susceptibility can occur and a "womb to tomb" lifetime study in laboratory animals was noted as a research need. There are no robust chronic data in the entirety of this database. Based on these considerations, another factor of at least 3-fold would easily be justified."

Response 6: It is not clear what was meant by "a clear trend in the data." There is no significant difference in the reduction of thyroidal iodide uptake produced by a given perchlorate dose between Day 2 and Day 14 (Greer *et al.*, 2002). OEHHA has decided not to apply an uncertainty factor for the short exposure duration in the Greer *et al.* study and database limitation in the final PHG risk assessment, based in part on the recommendations of the second University of California peer review.

Comment 7: *The commenter agreed with OEHHA in using the adult water consumption rate and adult body weight in converting the dose-response estimate to a PHG because*

pregnant women and their fetuses represent the susceptible population. It was also stated that "The PBPK simulations presented in the U.S. EPA (2002) draft demonstrate that uptake and elimination kinetics of perchlorate are such that the resultant HEE for adults and children are the same."

Response 7: A discussion of the PBPK results reported by Clewell *et al.* (2003a,b) and the modeling efforts of U.S. EPA has been added to the final risk assessment.

Comment 8: "The neurotoxicologists on the EPA expert panel were clear in their concern that the degree of thyroid hormone perturbation necessary to cause neurodevelopmental effects in laboratory animals is not well characterized, much less an interspecies comparison to humans, so that the assertion that rodents are much less [sic] sensitive than humans is unfounded with respect to the neurodevelopmental sequelae. Simply stated, the existing data in humans on the effects of perchlorate on thyroid hormones is inadequate to be informative. Neurodevelopmental evaluation of clinical subjects, notably sensitive life stages is not likely to pass an IRB so that the laboratory animal data must be relied upon. No neurodevelopmental indices have been evaluated in either the ecological epidemiological investigations of populations exposed to perchlorate or in the limited clinical studies."

Response 8: In the final PHG, it is stated that "…human adults are not as sensitive as rodents to the perturbation of thyroid hormones caused by perchlorate."

OEHHA agrees that there is a lack of epidemiological data on neurodevelopmental indices as endpoints of perchlorate exposure. However, if one can agree that adverse neurodevelopmental effects of perchlorate are mediated through thyroid hormone disruption, and that at the PHG level, there would not be a reduction in iodide uptake, then there should be no impairment of thyroid function. We agree that there is inadequate information to characterize potential direct effects on the fetus, but these would logically be related to reduction of iodide transfer across the placenta and iodide uptake into the fetal thyroid. The NIS in the placenta and the fetal thyroid are likely to be quite similar to that in the maternal thyroid. However, the lack of data on these effects in humans helps justify the use of a sensitive endpoint, maternal iodide uptake inhibition, and an appropriate uncertainty factor, for the PHG calculation.

Comment 9: *The commenter criticized OEHHA for not discussing the relationship between urinary iodine excretion rates and the percent iodide inhibition seen in the clinical studies that serve as the basis for the derivation of the PHG.*

Response 9: The relationship was not discussed because urinary iodine excretion data were not reported in the Greer *et al.* (2002) paper.

Comment 10: *The commenter suggested that there is a concern that reduced forms of perchlorate may enter the thyroid and that toxic effects of perchlorate should not be equated with iodide deficiency as a disease state.*

Response 10: There is a current scientific debate on whether perchlorate is translocated

into the thyroid cells and if perchlorate is reduced in the cells (De La Vieja *et al.*, 2000). If one agrees that NIS inhibition is the mode of action of perchlorate at low doses, resulting in decreased thyroid uptake of iodine, then one should agree that health effects resulting from perchlorate exposure could be similar to those associated with iodine deficiency. The nature and severity of effects are dependent on the perchlorate dose. At or below the PHG level, there should be no reduction in thyroidal iodide uptake and no perturbation of thyroid hormone balance.

Comment 11: *The commenter suggested* "This lack of reversibility for hormone changes and the duration-dependent changes in the other sacrifice points of the 90-day studies coupled with the observation of tumors in the F1 generation of the reproductive study collectively support a concern for the potential resetting of the HPT axis with prolonged exposure. This has profound implications for the lack of chronic data on this chemical and should be factored in to UF consideration."

Response 11: It is believed that thyroid hormone changes and thyroid tumors observed in the treated rats were mediated through the reduction of thyroidal iodide uptake and impairment of thyroid function. OEHHA contends that at the PHG level, such biological changes would be prevented in humans. In the rat developmental study described by the commenter, thyroid tumors were observed in two of the 30 rats in the highest dose group, treated at 30 mg/kg-day. No thyroid tumors were found in two lower dose groups at 0.3 mg/kg-day and 3 mg/kg-day, or in the control group. The BMDL (0.0037 mg/kg-day), the point of departure used by OEHHA in the perchlorate risk assessment, is approximately 8,000 times lower than the 30 mg/kg-day dose used in the rat study, which seems to us to provide an adequate margin of safety for this effect.

Comment 12: "It is not discernible at all to the naive reader that the Lawrence *et al.* (2001) study is in fact only a letter to the editor because it appears to be given as much weight and discussion as those that have been vetted in the peer reviewed literature. It also seems contradictory that the data from both of these studies are given much less scrutiny and reporting than some of the studies from the iodide deficiency literature which are not featured in the quantitative derivation. I again call attention to the serious deficiencies that precluded the use of these data for the PBPK model development noted in the QA/QC report (Merrill, 2001a). Similar reservations in relying on these data to calculate a level protective of public health would seem prudent."

Response 12: In the final PHG document, the dose-response evaluation was conducted using the thyroidal iodide uptake data reported by Greer *et al.* (2002). Study data reported by Lawrence *et al.* (2000, 2001) were not used. The Greer *et al.* (2002) study is published in a scientific journal and has gone through the usual peer review process. OEHHA is not aware of any "serious deficiencies" that could preclude the use of the data for human health risk assessment, as opposed to PBPK modeling.

Comment 13: *The commenter suggested that because inhibition of iodine uptake by the thyroid and other tissues appears to be competitive, the lower the iodine concentration*

relative to the perchlorate concentration (the higher the perchlorate/iodine ratio) the greater the inhibition. The effect level would be decreased in iodine-deficient individuals as compared to individuals on iodine-adequate diets, thus the intraspecies UF may not be adequate to cover sensitive subpopulations. This also argues against the designation of the 0.007 mg/kg-day dose as a NOAEL.

Response 13: There are no experimental data at doses relevant to environmental exposure that quantify NIS inhibition by perchlorate in relation to the serum perchlorate/iodine ratio. However, the commenter has provided no rationale for assuming that such an effect would require an intraspecies uncertainty factor greater than the default value of 10. OEHHA acknowledges that the threshold and NOAEL identified in a study are dependent on the size of the sample population as well as spacing of the doses used, and that a sample NOAEL is likely to be different from a population NOAEL. In our opinion, these uncertainties support the use of an intraspecies uncertainty factor of 10.

Comments from Jonathan Borak, Jonathan Borak & Company, Inc.

Comment 1: "The presence of an iodine-deficient sensitive subpopulation is hypothetical. The Draft provides no evidence that such a population exists in the US or California. To the contrary, the evidence provided suggests the absence of such a sub-population."

Response 1: Based on the NHANES III data, the population of the U.S. as a whole is not believed to suffer from iodine deficiency. However, the NHANE III data cannot exclude the possibility that a small percentage of the population gets less than optimal iodine from the diet. Due to the increased need of iodine in pregnant women, compared to the general population, women in pregnancy are more likely to get less than the optimal level of iodine. The same argument applies to lactating women.

Comment 2: "The Draft ignores the widely accepted WHO/INICEF/ICCIDD consensus criteria for iodine deficiency and offers no consistent alternative criteria. As a result, iodine deficiency in study populations is mischaracterized throughout the Draft." *An extensive discussion of the various studies is intended to demonstrate their differences in approach and characterization of iodine-deficiency states.*

Response 2: In the perchlorate risk assessment, OEHHA reported the descriptive characterization used by the authors of the studies. No attempt was made to make the descriptions adhere to a certain standard. It has been argued that while 24-hr and spot urinary measurements can be used to judge the overall iodine sufficiency of a population, they do not accurately reflect the iodine status of an individual. Therefore it is difficult to say whether a person is marginally or moderately iodine deficient, based on one or two urinary iodine measurements.

The inclusion of the studies is intended to show the range of adverse health effects that are known to be associated with iodine deficiency, hypothyroidism, and

hypothyroxinemia. It is clear that there is a continuum between the iodine-sufficient state and a severely iodine-deficient state, and that the degree of severity of iodine deficiency is related to the nature and severity of the adverse health effects.

Comment 3: "[T]he risk assessment has included substantial uncertainty by adopting the inhibition of iodine uptake as the critical effect. Because that critical effect is not expected to cause adverse outcomes except in sensitive sub-population, and because even in such cases the effects are hypothetical and may not occur, there is no need for an additional inter-individual uncertainty factor of 10."

Response 3: OEHHA acknowledges that there is an inherent margin of safety between reduction in thyroidal iodide uptake and impairment of thyroid function in healthy, iodine-sufficient adults. The size of this margin is expected to vary among individuals depending on a number of factors, such as dietary iodine intake, amount of iodide stored in the thyroid, and exposure to other goitrogens in the environment. The interindividual uncertainty factor of 10 applied in the risk assessment should account for the differences between the study population (Greer *et al.*, 2002) and the general population, including sensitive subgroups.

Comments from David R. Mattie, Air Force Laboratory, Department of the Air Force

Comment 1: *The commenter supports the use of a harmonized approach for determining the toxicity of low concentrations of perchlorate in drinking water to humans and the identification of fetuses of pregnant women with less than optimal iodine intake as one of the sensitive subpopulations.*

Response 1: No response required.

Comment 2: *The commenter also agrees with OEHHA's choice of Greer et al. (2002) as the critical study and their use of the lowest tested dose of 0.007 mg/kg-day as the threshold for iodide inhibition. As a perchlorate dose of 0.007 mg/kg-day produced no significant thyroidal iodide uptake inhibition in human, this level represents a NOEL and not a true NOAEL. The commenter noted that it is important to distinguish NOEL from NOAEL, and that using a NOEL in place of NOAEL is considerably more conservative.*

Response 2: OEHHA acknowledges there is an inherent safety margin between the NIS inhibition and thyroid hormone disruption. This margin of safety is expected to vary among individuals depending on many factors, such as dietary iodine intake, amount of iodine stored in the thyroid, and exposure to other goitrogens in the environment. OEHHA does not explicitly distinguish between a NOAEL and a NOEL for the PHG program, but considers the type and severity of effect in the choice of uncertainty factors.

Comment 3: *For most chemicals in the U.S. EPA's Integrated Risk Information System*

database, the customary procedure has been to use an "adverse" health condition. Therefore, OEHHA's use of iodide inhibition for the perchlorate risk assessment is inherently conservative. Because of this "built-in" level of conservatism, we cannot justify imposing an additional combined uncertainty factor (UF) of 30 (an UF of 10 to account for interindividual variability and an UF of 3 to account for limitations in the database).

Response 3: In the final perchlorate risk assessment, OEHHA has applied an uncertainty factor of only 10 from the iodine uptake inhibition level. The uncertainty factor is used to account for interindividual variability, including sensitivity of the fetus. Based on the recommendation of the second University of California peer review and other comments received, the uncertainty factor of three for limitations in the database is no longer applied (OEHHA, 2004).

Comment 4: *The commenter disagreed with the use of an UF of 10 for intraspecies variability to account for sensitive populations. The commenter indicated that assuming drinking water is the only source of perchlorate, extrapolation from the Greer et al. (2002) data supports a water concentration of 180-220 ppb. Based on the Crump et al. (2000) study of neonates and schoolchildren in Chile, TERA proposed a water concentration of 70 ppb. Furthermore, PBPK modeling of inhibition of thyroidal iodide uptake in adult rat, pregnant rat, fetal rat, lactating rat, and neonate rat indicates that intraspecies variability between adult rats and fetal rats is approximately 2. It was suggested that based on these data, human intraspecies variation for the most critical human subpopulation (fetuses) is predicted to be approximately 2.*

Response 4: In our opinion, there is considerable uncertainty in extrapolating the modeled rat data to the human sensitive subpopulations; variability within a rat strain raised under standard conditions on a standard iodine-sufficient diet is always assumed to be less than in a human population. In addition, there were only 37 subjects in the Greer *et al.* (2002) study. These subjects were iodine-sufficient and without any known thyroid problems. Sensitive populations were not represented in the study. Thus the variability observed in the study data is expected to be smaller than that in the general population. The default intraspecies uncertainty factor of 10 appears to us to be fully justified in this case. Concern over concurrent exposure to other goitrogens in the environment is another reason to avoid using an uncertainty factor below 10 in this particular case.

Comment 5: "Rat brain morphometry data (U.S. EPA, 2002) are not valid and should not be used or referenced in any risk assessment for perchlorate. The brains were not cut in a standardized manner, so the results are based on processing error rather than the effects of perchlorate."

Response 5: OEHHA realizes there are controversies in the interpretation of the rat brain morphometry data. In the final risk assessment, some of the different interpretations and disagreements are discussed**.** Despite the differing interpretations of these rat data, OEHHA believes that the animal studies as a whole indicate a reason for concern about potent neurodevelopmental effects of perchlorate.

REFERENCES

Andersen S, Pedersen KM, Pedersen IB, Laurberg P (2001). Variations in urinary iodine excretion and thyroid function. A 1-year study in healthy men. Eur J Endocrin 144:461-465.

Appleby PN, Thorogood M, Mann JI, Key TJ (1999). The Oxford vegetarian study: an overview. Am J Clin Nutr 70(3):525S-531S.

Argus Research Laboratories (2001). Hormone, thyroid and neurohistological effects of oral (drinking water) exposure to ammonium perchlorate in pregnant and lactating rats and in fetuses and nursing pups exposed to ammonium perchlorate during gestation or via material milk. Protocol no. 1416-003. Argus Research Laboratories, Inc., Horsham, PA.

Brechner RJ, Parkhurst GD, Humble WO, Brown MB, Herman WH (2000). Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J Occup Environ Med 42:777-782.

Caldwell DJ, King JH, Kinkead ER, Wolfe RE, Narayanan L, Mattie DR (1995). Results of a fourteen day oral-dosing toxicity study of ammonium perchlorate. Tri-Service Toxicology Consortium, Armstrong Laboratory. Wright-Patterson Air Force Base, Dayton, Ohio.

California Code (2002). California Health and Safety Code Section 116293(a).

Clewell RA, Merrill EA, Yu KO, Mahle DA, Sterner TR, Fisher JW, Gearhart JM (2003). Predicting neonatal perchlorate dose and inhibition of iodide uptake in the rat during lactation using physiologically-based pharmacokinetic modeling. Toxicol Sci 74:416-436.

Crooks J, Wayne EJ (1960). A comparison of potassium perchlorate, methylthiouracil, and carbimazole in the treatment of thyrotoxicosis. Lancet 1:401-404.

Crump C, Michaud P, Tellez R, Reyes C, Gonzalez G, Montgomery EL, Crump K, Lobo G, Becerra C, Gibbs JP (2000). Does perchlorate in drinking water affect thyroid function in newborns or school-age children? J Occup Environ Med 42:603-612.

De La Vieja A, Dohan O, Levy O, Carrasco N (2000). Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiol Rev 80:1083-1105.

Erickson EB (2003). Perchlorate found in Texas milk. http://www.mindfully.org/Food/2003/Perchlorate-Texas-Milk25sep03.htm.

Gibbs JP, Ahmad R, Crump KS, Houck DP, Leveille TS, Findley JE, Francis M (1998). Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. J Occup Environ Med 40:1072-1082.

Girling JC, de Swiet M (1992). Thyroxine dose during pregnancy in women with primary hypothyroidism. Br. J. Obstet Gynaecol 99:368-370.

Glinoer D, Delange F, Laboureur I, De Nayer P, Lejeune B, Kinthaert J, Bourdoux P (1992). Maternal and neonatal thyroid function at birth in an area of marginally low iodine intake. J Clin Endocrinol Metab 75(3):800-805.

Glinoer D, de Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grün J, Kinthaert J, Lejeune B (1995). A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. J Clin Endocrinol Metab 80:258-269.

Glinoer D (2001). Pregnancy and iodine. Thyroid 11(5):471-481.

Goodman G (2003). Personal communication. The influence of dietary iodine on the dose-response for perchlorate inhibition of thyroidal radioiodine uptake in humans: a modeling analysis of clinical exposure data. Draft. January 24, 2003.

Greer MA, Goodman G, Pleus RC, and Greer SE (2002). Health effects assessment for environmental perchlorate contamination: The dose-response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect 110:927-937.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell M, Hermos RJ, Waisbren SE, Faix JD, Klein RZ (1999). Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549-555.

Heyerdahl S (2001). Longterm outcome in children with congenital hypothyroidism. Acta Paediatrica 90:1220-1222.

Heyerdahl S, Kase FB, Lie SO (1991). Intellectual development in children with congenital hypothyroidism in relation to recommended thyroxine treatment. J Pediatr 118:850-857.

Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ (1998). Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). J Clin Endocrinol Metab 83:3401-3408.

Kaplan MM (1992). Monitoring thyroxine treatment during pregnancy. Thyroid 2:147-152.

Kirk AB, Smith EE, Tian K, Anderson TA, Dasgupta PK (2003). Perchlorate in milk. Environ Sci Technol 37:4979-4981.

Klein RZ, Sargent JD, Larsen PR, Waisbren SE, Haddow JE, Mitchell ML (2001). Relation of severity of maternal hypothyroidism to cognitive development of offspring. J Med Screen 8:18-20.

Knudsen N, Bülow I, Laurberg L, Ovesen L, Perrild H, Jørgensen T (2002). Association of tobacco smoking with goiter in a low-iodine-intake area. Arch Intern Med 162:439-443.

Kung AWC, Lao TT, Chau MT, Tam SCF, Low LCK (2000). Goitrogenesis during pregnancy and neonatal hypothyroxinaemia in a borderline iodine sufficient area. Clin Endocrinol 53:725-731.

Lambers AC, Koppeschaar HPF, van Isselt JW, Slob W, Schothorst RC, Mensinga TjT, Meulenbelt J (2000). The effect of nitrate on the thyroid gland function in healthy volunteers in a 4-week oral toxicity study. National Institute of Public Health and the Environment, Bilthoven, The Netherlands. RIVM report 235802 015. Available at: http://www.rivm.nl/bibliotheek/rapporten/235802015.html.

Lamm SH, Braverman LE, Li FX, Richman K, Pino S, Howearth G (1999). Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. J Occup Environ Med 41:248-260.

Lamm SH, Doemland M (1999). Has perchlorate in drinking water increased the rate of congenital hypothyroidism? J Occup Environ Med 41:409-413.

Laurberg P, Nohr SB, Pedersen KM, Fuglsang E (2004). Iodine nutrition in breast-fed infants is impaired by maternal smoking. J Clin Endocrinol Metab 89(1):181-187.

Lawrence JE, Lamm SH, Pino K, Richman K, Braverman LE (2000). The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid 10:659-663.

Lawrence J, Lamm S, Braverman LE (2001). Low dose perchlorate (3 mg daily) and thyroid function. Letter to the Editor. Thyroid 11 (3):295.

Li FX, Byrd DM, Deyhle GM, Sesser DE, Skeels MR, Katkowsky SR, Lamm SH (2000). Neonatal thyroid-stimulating hormone level and perchlorate in drinking water. Teratology 62:429-431.

Lieberman CS, Pino SC, Fang SL, Braverman LE, Emerson CH (1998). Circulating iodide concentrations during and after pregnancy. J Clin Endocrinol Metab 83:3545-3549.

Lightowler HJ, Davies GJ (1998). Iodine intake and iodine deficiency in vegans as assessed by the duplicate-portion technique and urinary iodine excretion. Br J Nutr 80(6):529-35.

Lind P, Langsteger W, Molnar M, Gallowitsch HJ, Mikosch P, Gomez I (1998). Epidemiology of thyroid diseases in iodine insufficiency. Thyroid 8(12):1179-83.

Milakovic M, Berg G, Eggertsen R, Lindstedt G, Nystrom E (2001). Screening for thyroid disease of 15-17-year-old schoolchildren in an area with normal iodine intake. J Intern Med 250(3):208-212.

NAS (2001). Dietary reference intakes for Vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academy Press, Washington, D.C.

OEHHA (2000). Air Toxics Hot Spots Program Risk Assessment Guidelines. Technical Support Document for Exposure Assessment and Stochastic Analysis. Part IV. September 2000. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Available at: www.oehha.ca.gov/air/exposure_assess/index.html.

OEHHA (2004). Scientific peer reviews of the Office of Environmental Health Hazard Assessment's December 2002 Draft Public Health Goal (PHG) Document on Perchlorate in California Drinking Water. Review comments are available at: http://www.oehha.ca.gov/

Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Larsen KR, Eriksen GM, Johannesen PL (1993). Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. J Clin Endocrinol Metab 77:1078-1083.

Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL (1999). Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 50:149-155.

Rillema JA, Rowady DL (1997). Characteristics of the prolactin stimulation of iodide uptake into mouse mammary gland explants. Proc Soc Exp Biol Med 215:366-369.

Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P, Cappa F, D'Armiento M (1991). The effects of iodoprophylaxis on thyroid size during pregnancy. Am J Obstet Gynecol 164:482-485.

Rotondi M, Amato G, Biondi B, Mazziotti G, Buono AD, Nicchio MR, Balzano S, Bellastella A, Glinoer D, Carella C (2000). Parity as a thyroid size-determining factor in areas with moderate iodine deficiency. J Clin Endocrinol Metab 85:4534-4537.

Rovet J, Ehrlich R, Sorbara D (1987). Intellectual outcome in children with fetal hypothyroidism. Implications for neonatal diagnosis. Pediatr 110:700-704.

Rovet JF (2000). Neurobehavioral consequences of congenital hypothyroidism identified by newborn screening. Therapeutic outcome of endocrine disorders. Efficacy, innovation, and quality of life. Stabler BB, ed. Springer-Verlag, New York, NY, pp. 235-254.

Schwartz J (2001). Gestational exposure to perchlorate is associated with measures of decreased thyroid function in a population of California neonates. Master's Thesis. University of California, Berkeley, California.

Smith PN, Jackson WA (2003). Perchlorate in the environment: ecological considerations. Presentation material available at website: www.tribalwater.net/perchlorate/Martinez.pdf

Smyth PP, Hetherton AM, Smith DF, Radcliff M, O'Herlihy C (1997). Maternal iodine status and thyroid volume during pregnancy: correlation with neonatal iodine intake. J Clin Endocrinol Metab 82(9):2840-2843.

Song S DD, Rovet J (2001). The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. J Develop Behav Pediatr 22:376-384.

Spitzweg C, Joba W, Eisenmenger W, Heufelder AE (1998). Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa. J Clin Endocrinol Metab 83:1746-1751.

Springborn Laboratories (1998). A 90-day drinking water toxicity study in rats with ammonium perchlorate. June 3, 1998. Study No. 3455.1. Springborn Laboratories, Inc., Health and Environmental Sciences, Spencerville, OH.

Stanbury JB, Wyngaarden JB (1952). Effect of perchlorate on the human thyroid gland. Metabolism 1:533-539.

Tamaki H, Amino N, Takeoka K, Mitsuda N, Miyai K, Tanizawa O (1990). Thyroxine requirements during pregnancy for replacement therapy of hypothyroidism. Obstet Gynecol 76:230-233.

U.S. EPA (2000). Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). Office of Water, U. S. Environmental Protection Agency, Washington, DC. EPA-822-B-00-004.

U.S. EPA (2002). Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (External Review Draft). Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. NCEA-1-0503.

van den Hove MF, Beckers C, Devlieger H, de Zegher F, De Nayer P (1999). Hormone synthesis and storage in the thyroid of human preterm and term newborns: effect of thyroxine treatment. Biochimie 81:563-570.

van Maanen JMS, van Dijk A, Mulder K, de Baets MH, Menheere PCA, van der Heide D, Mertens PLJM, Kleinjans JCS (1994). Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicol Lett 72:365-374.

van Vliet G (1999). Neonatal hypothyroidism: Treatment and Outcome. Thyroid 9:79-84.

Versloot PM, Schroder-van der Elst JP, van der Heide D, Boogerd L (1997). Effects of marginal iodine deficiency during pregnancy: iodide uptake by the maternal and fetal thyroid. Am J Physiol 273:E1121-E1126.

Yu K, Mahle D, Narayanan L, Godfrey R, Todd P, Parish M, McCafferty J, Ligman T, Sterner T, Butler G, Mattie D, Fisher J (2001). Tissue distribution and inhibition of iodide uptake by perchlorate in pregnant and lactating rats in drinking water studies. Abstract No. 1386, presented at the 40th Annual Meeting of the Society of Toxicology, March 25-29, San Francisco, CA. The Toxicologist 60(1):291-292.